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Yan et al.

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(54) **ENHANCEMENT OF NITROGEN USE EFFICIENCY IN WHEAT AND OTHER PLANTS**

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Related U.S. Application Data

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(51) **Int. Cl.**

C12N 15/82	(2006.01)
C07K 14/415	(2006.01)

(52) **U.S. Cl.**
CPC ***C12N 15/8243*** (2013.01); ***C07K 14/415*** (2013.01); ***C12N 15/8261*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

PUBLICATIONS

Chen et al (2009) Theoretical and Applied Genetics 118: p. 881-889.*

* cited by examiner

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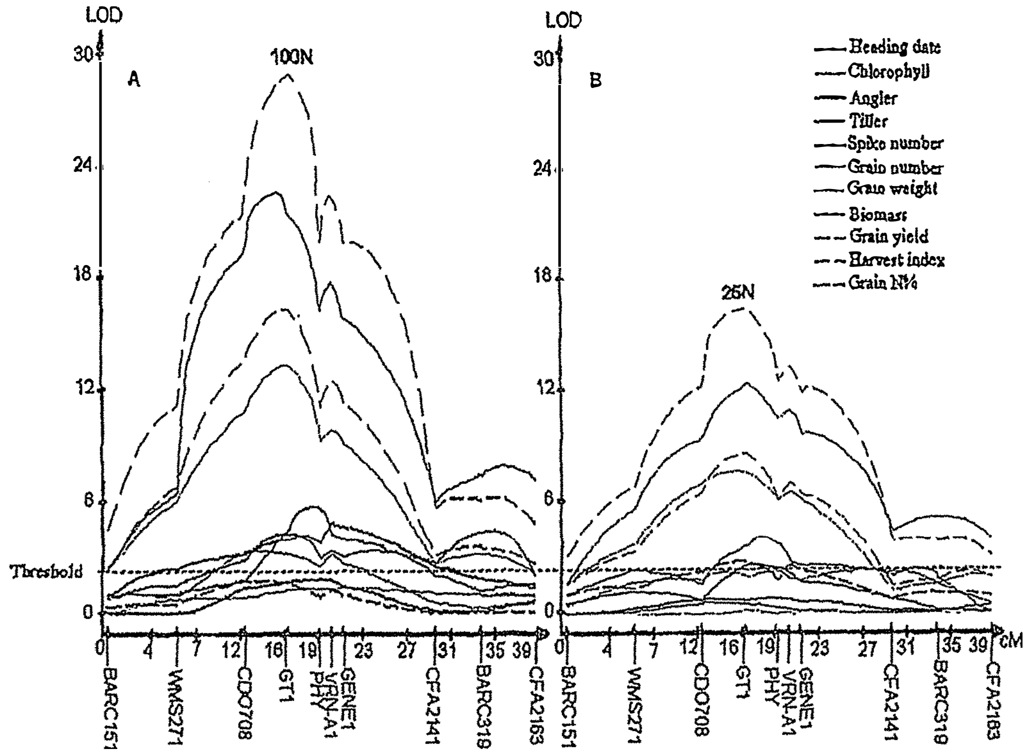
(57) **ABSTRACT**

Genes associated with nitrogen utilization efficiency (NUE) in plants are provided. The gene $VRN1^{N}$ was identified as TaNUE1 in chromosome 5A of the wheat cultivar Jagger and is encompassed by quantitative trait locus Qnue.osu-5A. $VRN1^{N}$ is regulated by nitrogen is associated with enhanced NUE by plants which contain the gene. In addition, the gene ANR1 from wheat cultivar Jagger has also been identified as involved in nitrogen metabolism. Methods for genetically engineering plants to contain and express one or both of $VRN1^{N}$ and ANR1 are also provided, as are genetically modified plants that have been transformed with one or both of the genes, and plants that have been bred conventionally and selected for the presence of one or both genes.

5 Claims, 42 Drawing Sheets

Specification includes a Sequence Listing.



LOD
100N
A
B
25N
Threshold
Heading date
Chlorophyll
Angler
Tiller
Spike number
Grain number
Grain weight
Biomass
Grain yield
Harvest index
Grain N%
cM
BARC151
WMS271
CDO708
GT1
PHY
VRN-A1
GENE1
CFA2141
BARC319
CFA2163

FIG. 1

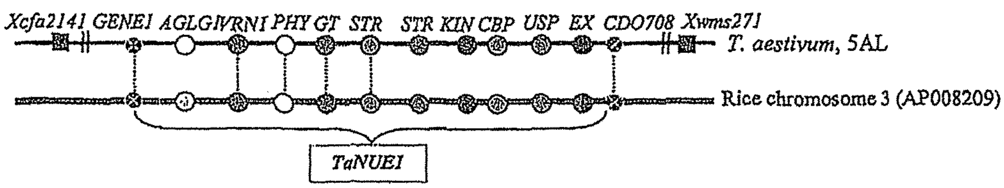

Xcfa2141 GENE1 AGLG1VRN1 PHY GT STR STR KIN CBP USP EX CDO708 Xwms271
T. aestivum, 5AL
Rice chromosome 3 (AP008209)
TaNUE1

FIG. 2

FIG. 3A

AAACCTTGGACCTAACCCTCTGTAGAAACCTTTCCATCCATCTTCAGCGATCAATCTTCTAACTACCTCAC
TGGCTTTTGGCTTGTTTTGATTAACCTAGATGAAAAAACAGAAAAAAAATATTAATGTGGCTGATATAAAA
CCATAATTCGCAGGATGCATGTACAGTTAAGAAATAGAAAAAAAATGCAAATTCTGATGACATAAAGAAAA
CATCAGCTGCACGGAGCATTTTCTTAAAGCATCACCAGAAAAATTGAACACTGGGGGTTGAACGCTACAGT
CTAGAAGTGTGATTGTAATTAACTAAAAGTCTACACTCGACACTATCAACACAGATAAAACATGTAATGTT
AAGAAAGTTGTGAA (SEQ ID NO: 1)

FIG. 3B

AAACCTTGGACCTAACCCTCTGTAGAAACCTTTCCATCCATCTTCAGCAATCAATCTTCTAACTACCTCAC
TGGCTTTTGGCTTGTTTTGATTAACCTAGATGAAAAAACAGAAAAAAAATATTAATGTGGCTGATATAAAA
CCATAATTCGCAGGATGCATGTACAGTTAAGAAATAGAAAAAAAATGCAAATTCTTGATGACATAAAGAAA
ACATCAGCTGCACGGAGCATTTTCTTAAAGCATCACCAGAAAAATTGAACACTGGGGGTTGAACGCTACAG
TCTAGAAGTGTGATTGTAATTAACTAAAAGTCTACACTCGACACTATCAACACAGATAAAACATGTAATGT
TAAGAAAGTTGTGAA (SEQ ID NO: 2)

FIG. 4A

TGCAGCATCCTCCTTCCAGATTAGTGTAGGTCTTGCTGGGACTACCAATAAGACGGTTAAGATGCCGAAAA
ACTTCACCCTTAGGGCCCCAGGTCCGGGGTACACATGTGGGCGTGCTCTTGTTGGCAGGCCTACCAAGTAT
TACTCGTCAGACGGGCGCAGGGTAACCCAAGCTCTCAGTAAGTTGCCCACTTATTGCTCTTCACTGCTTGC
TCTATATTGCTTTAATACTTTGCGCAAATGCATTAGCAAGCTACACTAATTGAGCTAAACACATCTTAGTA
CCACTTTTGTACGTTTCTGCTCCTTAATTGTGAATGAATTTTATGTTATAATATGTGTAGGATTAGTGAAA
GACTGAAAGGAGTGAAACCATTGAAATCGGAAGTGATTCATTTTCGAGAGGAGATGAGTTCATCACCTAGG
ATCGATGTTAGCTCATATTTATTTGAAAATAAGCCACCACTAAGCCTGATAATATCTTAACTAGTTTTGTT
CACTTGCAAATAATGGATTTCAAATGCAGGAAACATC (SEQ ID NO: 3)

FIG. 4B

TGCAGCATCCTCCTTCCAGATTAGTGTAGGTCTTGCTGGGACTACCAATAAGACGGTTAAGATGCCGAAAA
ACTTCACCCTTAGGGCCCCAGGTCCGGGGTACACATGTGGGCGTGCTCTTGTTGGCAGGCCTACCAAGTAT
TACTCGTCAGACGGGCGCAGGGTAACCCAAGCTCTCAGTAAGTTGCCCACTTATTGCTCTTCACTGCTTGC
TCTATATTGCTTTAATACTTTGCGCAAATGCATTAGCAAGCTACACTAATTGAGCTAAACACATCTTAGTA
CCACTTTTGTACGTTTCTGCTCCTTAATTGTGAATGAATTTTATGTTATAATATGTGTAGGATTAGTGAAA
GACTGAAAGGAGTGAAACCATTGAAATCGGAAGTGATTCATTTTCGAGAGGAGATGAGTTCATCACCTAGG
ATCAATGTTAGCTCATATTTATTTGAAAATAAGCCACCACTAAGCCTGATAATATCTTAACTAGTTTTGTT
CACTTGCAAATAATGGATTTCAAATGCAGGAAACATC (SEQ ID NO: 4)

FIG. 5A

CGAGATGCCGACGCTGACGAAGCTGTACAGCATGAAGGAGGCCGCCCTCCACAACACCCCCGACGACTGCT
GGATCGTCGTCGACGGCAAGGTAGCGCCTCCCTCATACCCCTCGCCGCCGATCTGGCTTCAGCAATACTGC
CCCTAACATCGGTAGGTAGGTAGGTAGGGTCTAGGGTGTATGGACGCGTTTCGTTGTTGCTAGTTGGGCTT
CGACCCCCGCCCTTAGCCTGTTCGACCGAATGCCTGGGAGATCCCGCGCTCGCTTTGTTAGTGAGAAGGCT
GCAGGAATCGAAACCGAACGTCTCTGCGAGTGGCGTGGCCTGCTAGTCACCTCGTGGGGCAGTTGTGCTGG
GGTATCCTCTGTTGAAGGCAACCACAGCAGATGCCTCTGTTGAGGGCTTTGAATCAAATAGAATTTGTGTC
AGCAGAGAGTAGATACGCATTACAATACTACCTGGCAAATATGTTCCACTACTCTGATTCTGTGGCGAGCT
CATGCCCTGTTGATGAATACAATGCAGATTTATGATGTGACCGCGTATTTGGATGACCATCCTGGGGGTGC
TGATGTGCTGCTTGCCGTGACTGGTACTACTTCTCAGTTCTCACCTCTTGTTTTCATGTTCTTGTTCAGCA
CATTTTAGTTTCTCATAGGCTGTCTGCTCATACATGATAATCTGTTTCAAGGTATGGATGGCACCGAGGAA
TTTGAAGATGCGGGCCACAGCAAGGATGCCAAGGAGTTGATGAAAGATTACTTCATTGGGGAGTTGGACTT
GGACGAAACACCTGACATGCCTGAGATGGAGGTTTTCAGGAAAGAGCAGGACAAGGACTTCGCCAGCAAGC
TGGCGGCTTACGCTGTGCAGTACTGGGCCATTCCGGTAGCAGCAGTTGGGATATCAGCCGTGCTTGCTATA
TTGTATGCTCGAAGGAAGTGATGATCGGTTATAGGTTGATTGAAGGACCATTTTGGGGTAACCAACACATT
TATAGCTGGTTATGGATGGAGAGATTATGTACTTCTGTCCAAAGGGGAAGACACATTGCTGTATTGAGCCC
TTAGGTACTTGAGTCAAATATTTGTCCACAAAATTGGTGGTACTATTTTGTCAATATGTCATTCAATGGAT
AGATTCATTTCAAGACCTGAACCATGTGTGTGATGTAAACCCTCTTACGCCTTGAGGCAGCTGCTGGCGCA
GATTTCTTCCGTGCCATTATTGCTTCTATTTTTGTTATTTTCGTGGGATGTGCCACGGTACTGCTATTTCT
GAATATTGTGATTTTTCAATCCCTCACTTGCTCCTGAATAACCCTGAAGACTTTTGTGTAACTTGTTCTTT
TGTAACTTTCAAGATGCAAATTGGGATTTGTTGGCCCCTCCTTTTGAGTCGACATTTGTTGAAAGCTTCCC
GTGCAAGCATTTCATCCATATATTTTCCTATTCGTTTTTCTTCCCCTTGTGTCACCTCACAAGGTGTAGAT
AGTTGGGCAGTAGACTTCAGAAAGATAGCAGGTAGCTTTTGCCGCCCCCTCTCTTGATATTTCTAAACTGG
GGTTGCTTCGCCATCACTACGTAATACTAGTTGAAGAAATTTTATCATGTGCTACTGCTGTGCTTAGTAAC
CTAGCACCTGGGTTCGACACAGCCTCTTGGCATTGCATTGTGCAGATAAGGCTTGCCTCAATGCCTTGTAT
AATCCTTCCCCAGGTGTCACCTGGAAATGTACACCTTACCTGATAGTATTATGCAGGGGTATCACTTGGAA
TTGATGGTGTTGCTTGAAGGCAGAGCAAAAAACCAACATGTGGAAGGTGGTGCTGAGCTTCTCAACC
(SEQ ID NO: 5)

FIG. 5B

CGAGATGCCGACGCTGACGAAGCTGTACAGCATGAAGGAGGCCGCCCTCCACAACACCCCCGACGACTGCT
GGATCGTCGTCGACGGCAAGGTAGCGCCTCCCTCATACCCCTCGCCGCCGATCTGGCTTCAGCAATACTGC
CCCTAACATCGGTAGGTAGGTAGGTAGGGTCTAGGGTGTATGGACGCGTTTCGTTGTTGCTAGTTGGGCTT
CGACCCCCGCCCTTAGCCTGTTCGACCGAATGCCTGGGAGATCCCGCGCTCGCTTTGTTAGTGAGAAGGCT
GCAGGAATCGAAACCGAACGTCTCTGCGAGTGGCGTGGCCTGCTAGTCACCTCGTGGGGCAGTTGTGCTGG
GGTATCCTCTGTTGAAGGCAACCACAGCAGATGCCTCTGTTGAGGGCTTTGAATCAAATAGAATTTGTGTC
AGCAGAGAGTAGATACGCATTACAATACTACCTGGCAAATATGTTCCACTACTCTGATTCTGTGGCGAGCT
CATGCCCTGTTGATGAATACAATGCAGATTTATGATGTGACCGCGTATTTGGATGACCATCCTGGGGGTGC
TGATGTGCTGCTTGCCGTGACTGGTACTACTTCTCAGTTCTCACCTCTTGTTTTCATGTTCTTGTTCAGCA
CATTTTAGTTTCTCATAGGCTGTCTGCTCATACATGATAATCTGTTTCAAGGTATGGATGGCACCGAGGAA
TTTGAAGATGCGGGCCACAGCAAGGATGCCAAGGAGTTGATGAAAGATTACTTCATTGGGGAGTTGGACTT
GGACGAAACACCTGACATGCCTGAGATGGAGGTTTTCAGGAAAGAGCAGGACAAGGACTTCGCCAGCAAGC
TGGCGGCTTACGCTGTGCAGTACTGGGCCATTCCGGTAGCAGCAGTTGGGATATCAGCCGTGCTTGCTATA
TTGTATGCTCGAAGGAAGTGATGATCGGTTATAGGTTGATTGAAGGACCATTTTGGGGTAACCAACACATT
TATAGCTGGTTATGGATGGAGAGATTATGTACTTCTGTCCAAAGGGGAAGACACATTGCTGTATTGAGCCC
TTAGGTACTTGAGTCAAATATTTGTCCACAAAATTGGTGGTACTATTTTATCAATATGTCATTCAATGGAT

FIG. 5B (con't)

AGATTCATTTCAAGACCTGAACCATGTGTGTGATGTAAACCCTCTTACGCCTTGAGGCAGCTGCTGGCGCA
GATTTCTTCCGTGCCATTATTGCTTCTATTTTTGTTATTTTCGTGGGATGTGCCACGGTACTGCTATTTCT
GAATATTGTGATTTTTCAATCCCTCACTTGCTCCTGAATAACCCTGAAGACTTTTGTGTAACTTGTTCTTT
TGTAACTTTCAAGATGCAAATTGGGATTTGTTGGCCCCTCCTTTTGAGTCGACATTTGTTGAAAGCTTCCC
GTGCAAGCATTTCGTCCATATATTTTCCTATTCGTTTTTCTTCCCCTTGTGTCACCTCACAAGGTGTAGAT
AGTTGGGCAGTAGACTTCAGAAAGATAGCAGGTAGCTTTTGCCGCCCCCTCTCTTGATATTTCTAAACTGG
GGTTGCTTCGCCATCACTACGTAATACTAGTTGAAGAAATTTTATCATGTGCTACTGCTGTGCTTAGTAAC
CTAGCACCTGGGTTCGACACAGCCTCTTGGCATTGCATTGTGCAGATAAGGCTTGCCTCAATGCCTTGTAT
AATCCTTCCCCAGGTGTCACCTGGAAATGTACACCTTACCTGATAGTATTATGCAGGGGTATCACTTGGAA
TTGATGGTGTTGCTTGAAGGCAGAGCAAAAACCAACATGTGGAAGGTGGTGCTGAGCTTCTCAACC
(SEQ ID NO: 6)

FIG. 6A

GAGGTCGGAGGTCGGAGATGGGTCGCGGCAAGGTGGTGCTGCAGCGGATCGAGAACAAGATCAGCCGCCAG
GTGACGTTCGCCAAGCGCCGCAACGGCCTGCTCAAGAAGGCCTACGAGCTCTCCCTCCTCTGCGACGCCGA
GGTCGCGCTCGTCCTCTTCTCCCACGCTGGCCGCCTCTACCAGTTCTCCTCCTCCTCCAAGTAATTACTCC
TTCCGATCTCCCCCAGTGCCGTACCATATCGATCCCTCCATTTCCTTTTCTCTTTGTGGTTTTGCCGAGTC
GATCCTTTTGATTTGCTCTCCCCGTTCAAACATTTTGTCCATACGCGACGTTCGATCTGAATTTTCTTGCG
TCTTAGGGCGTCCGTGCATGAACTTATGGGGGGCTGGGTCCGTACGTTCTTTCCCTCTTGTTTGCTGTTCT
GTTGGCCACTGTGTCAAAAGAGGCTAGCAAGAAACAAACAAAGGAAAAAGTGATGAGCTCACCCGCAGCAG
CAGATCGACGGACATACTATGCAGTAGGAGTATATGTCATGCGTATGTTTGTCTCATTCACAGTAGAGGAT
TAAAAAGGGGTTTTAATCTAAAAAAAAACAAGAAGAAAAGATGTTTTTATTTGATGTACGCCTGACCACACC
TGTATTGAGGATACATGTATGCACATAATTAGAGCTTTGATCACCTGCTGAGATTAATTTGCACCAATATG
GCATGCATCCTTGTGAAACTCATACGGGCACTAATTGTTTTTCTACAAATTTTATCTAGCTTTGTCTTATG
GTCTGGGTAGTATGATGATCCACTTCTGAGAATTAATTTGAATTATGTAATTTTAAATACTTTTCTGCAGA
CCCAAGTTCAATCTATTTTTTTTTCTCAAAACAAAGGTTCAGTCTAATTTGACACCTTTAAGGCGTAGGATT
GAATTATATATATGCTTGTTTAATGTTATTTGTCAAAGAACTAAGAAAGGATATATACCGCTTTCAGTTAACT
GAATTGCATTAATTTTCTAGTCAAAGTACCGAAATAATACTATTGAAAAAAATGAAACAGTTAAGTGCTTT
AATTCAACTGTGGCCTTACATGATGTGACAGGGCAAGTGCTGCATCATATGTACTAGGTACAAATGAAGTG
CTATTTGTACTTCCTTGGAGCAAAAGAAAACAAGTAATAAACTAGCTAATGTTAGGTTCGTACCTACTCCC
TCCGTCCCATAATGTAAGACCTTTTTTAACACGGTCTTATATTATGGGATGAAAGGAGTACGCAATAATTT
AAGCAGCTCTATAGGGTAGCATTACCTAATGATATCAGAACTTTATGTATGTTCGAGTCAAATATAGCTAG
GTTTTAATCTGTCAAAATTATAAAGCCACTGAGTTTGCTCAAAAAGTTTGTAAAAGCGCTGATACATGAAA
TGTGAAACCAGACTTGGTAAAATTGCATGCTAATATTTTGTAGGGCCAATCATGATTACTACTTGTCAGTT
CTATACAAACATGCCACTGGTGGCTAGCTTAAACTTTGTAGCAATTTTGGCTGAAATAGCTTTTTTGGTGA
AAATTAACAACTGTACTTCTCACAGTAGTAGCTCAATAAACATTCTTACAGTGGCATAGTTCTCCCAAAAG
TTTAATTAGTCAAAGGAAACAGATATGTCTTCTTTTTTATATAATGGAAAGTTCTTTTTAGGTACATCGTC
AAGTCTTCACTAGATTGTGATGTTTACACAACTTTGAAGCCATGTGTCAATGGCTATAAAGTGACCAAAAA
TTAGCTCAAAAGACTAAGACAACATATAGAATTTGTTAGAAGTTGAACATACAGAAAGTTTATTATGCGAG
AGACCTTCATTGTCCAATAATTATCGAATTCTGTCATGTAAATAGTGATACTTAGTTTCTAATCCCTCCCC
CTCCCCCAGTGAATCTGAATTTATGTTATTTACCTATGCGTGTACTTGCACAACTTAATCTCGAATTTTCA
ACTCATCGCAGCATGCTTAAGACCCTCGAGAAGTACCAGAGGTACATTTTCGCTTCCCAAGATGCTGCCGT
GCCGACTACCGATGAGATGCAGGTCTGAGGCTTTTATTCCCAATGCGCATATTATGAAGATTCTACAAATT
TTCCTCAGATACAACATCTTTGAATTTTTAACTAGCAGGTTATCAGAGAAATTTGTTTTCCTTCGTAGAAC
AATGTATCTATAATGCCCTAAATAACATATATAAATTGATTTTTGTGAAGAGATAAAACATTCAGTCATAC
ATTTAAAATATTTCATTCTGTATGACGTACGTTATATGAAGCATTGCCTATTCGTAAATGTTACCTAGTTC
ACACATGATTGCTAAAAGGTATTTCTCTGCTGGTAAAGGTGTTATATTTCCGTGTTTAGAACATGGATTTC
TGTTGCTTGTCATATAGGCAGTGAACTAATTATTTTGTTTGACTTTTTTATGTAAAATTACTGCCTTGTAA
ACATGCCCACATGGTTTGAAGCAAAAGATAAACCTTTGATAAATTTTTAGCAGTTACAAAATATTAAATGG
GAATGTAAGTTCATGGCAATTAGAATGTTGGAAAGTACAGCTAGAGCATTGGCCCAGTGCATTTCATGCAT
ACGCGCAGCATAATTCACGTACGTGGCTATCTATGTGAAATACAGCATCGAGTAACTGGGCACTGGGGAGA
CCTATATCTGCGCATGTTCCTTGAATTATCGCTAATGTACATGCATTTTGTGGTTGGTTATAACTTATAAG
TAGACTAACAGCTTGGTTGGCCACCACATGCAGTATTGTAGCAGATAGCAGCTTCAGACTGATTGGCCATA
TGCCATATACCTGCTGATGAGTTTATTACAACAGTGGAATGTATTAAAATTGATAAATACAATATGGCTAT
ATGTTATATGGTATAAATGTGGTAGTTGTTTATTAAAAAGGCATGGGGTAAAATGTTCAATTTATGTTTAG
TAGAGCCTAAGCTATGGTACGCCTTCTTCATGGTCACGGTCATATTTTCCAAATGACATGTCCAAAAGAAT
AGATTTGGACTTACTAGATCCTTTACTATTCATGCGAGAATTTATTGTTTATGAGGATTCACACACAGAGA
GTTGCCAGTATGTAATTTTTAGGATTCATGGTACAATTTAATCATAATCTTAATTGCTAGAACGTGTACTA
ATTTCTTTAGAAGATGGCAAGTGGGAACCTATAAACACACGAAGCAAGAACCATATGAACTCAACACAAGC
AATCAACTAAGCCATAGCAAAGCGCAAACAAGAGAACATTGATAGATGATTGGTTTCCCTAACGCTAGATC

FIG. 6A (con't)

GTAGTGTAGATGAACAATCCAAGTGCTAGAAGTTGCGAGAGAGTGACAATATGACTCGTTTGATCTCTTGA
TGTTGTGTAGAAAGGGAGCCGCAGTTGGGTTCATCTTCTTTTTCCGATAAACTTGGGTTCATCTTCATAG
TCATGATTATGGCATGCTCATGTCAAATCTTATGACATATAGTAAAACAAAGGTCTTCTGCGCACAATAAG
GATATCGAAGTATAACAAAAGGTTCACACGAATTGCTCTAGGATTTTTCAGTGATGTGGTACTCCAAGTTT
TTATTCTAGGAAGTATTCCTAGATTTATGGTATAAGTTGGTATATATTAACTCTTCAGTCATAATCATCTC
CAAGGTGATACTTTGACCATTTGTTTTTTTTCTTCTTTTTGCGACTGAACTATCAATTTCTATAAAAAATA
TGTTGATACACATAAAACATTTTACTCATTATGGAATTATGTTCTGCGATAATTCAAATATCTGTGTCAAA
TGTTTGTAATTTTATTTTTATTTTTACTGATAATCAGATTAAGAGTGCTTGCTGTTTTTTTTTTTGAAATG
ACCTATACTATGTGACTCATATGAAGGGGTACTCCTAGCTTGTAATCTTACAAAGTCGTCCGGGATTTATG
TTTAAAATTTTTAAATATTACCTCTTGTGTCATAATGTAGGTTGTCTCCAGCACGTGATACTTTGACAATC
AGTTTCCATAACAATATGCTGGTTCAAATGAAACATGGTACACTTTATAGATTATGTTTCACGACAACGTA
AATTTTGTTTCACGTTTTGTAAGTTTCTTTTTTTTTATGATGAAACCAAGAATGTTTGACGGACACAACTT
TGGAATTGTCCTACAATGTTACTCACATGAAGTATTTGATTTTTGCGGGACAAAAAGGCATTTTTCTTAAG
CTTTTATTTTTGCAGGACAAAATGGCATTTTTCTTAAGTTTACTTGATTTAGCATTTTCCCCATATCTCCT
TCTTTACACTAACTGCAGAATACACTAACTGCAGAACAACTATCTGGAGTATATGGAGCTGAAGTCAAGAG
TTGAGGTTTTACAACGCTCACAAAGGTGATGTTTCTATATTCCTCTCAGATAATTGCTCATTAATTTCAGC
AGGTTACCGCAACATTTGCTATGTTTGCTAAAGTAAGTACTGTTGATGGTGCCACAGGAATCTCCTAGGCG
AGGATTTGGCTCCACTGAGTACAATCGAGCTTGAACAGCTTGAGGGTCAAGTAGGCAAGACCTTGAGGCAA
ATAAGGTCAAGAAAGGTAAACTACATAGCAATAAAAAAAGTTAAGAGTATAAGTAGAAATTAGGTTAATCT
GCTAAAATCCATTCGTCTTATCGAGCAACGCTTGCTGCTAGTTTCACTAACTAGTGTCCATGATTTAACCT
GTACCACAGACTCAAGTACTGCTGGATGAAATGTGCGACCTGAAGAGAAAGGTAGCACTAAAAATACTTTC
CATTTCTGTTGCTAAATGATGGACGATGTCCTATTCCGTAGCTTCAAGCACAATCTTGTTTTGCAGGAGCA
AATATTGCAGGATGCAAATATGACCCTGAAAAGAAAGGTAACATGACCCAAATCATTTTTCCTAGCTAGAA
AGGTCTGCATTTGTACGCACGTAGCTAGGGAGGGACCATCCTCAAGGAGAAGCTGTCTCATTTCACTTGGG
CCAGTGACAAGTGATTGGAAAGTTGATGACTCGGCAAGCCCACTAGTAGTTAGTTAGTAGGCAGGGGACCC
CTGGTTGGCACCACAGTATAAACACAGGTGGCTTTCAGGTACCACCAATTGCAGCTACCTGCCGTGTTTAT
GTGTGTTTGTGCACTGCAAGCATTCTTCTTCTTCCTGGCTTTCAGAAAATCACTCTTCTTGTTTTTACCCT
CTACTGAAAACGGCTTCATCCATTGGTGTATGTAATGCTCTTGATCACTCCCGTTTCACTTCAGCTGGGCG
AGATCGAGCTGGAGGCGACACCTGATCCCCCGCAGCAGCCGCAGCAGCAGCAGATGTGGCAGGGCGACCGG
GGCGTGCCGCCCCACACGCCTCCGCAGCCAGAGCACTTCTTCCAGGCCCTAGAACGCTATCCTTCCCTGCA
GCCAGTGTAAGACTTCTAACTCTTTTTTTCCTTTTCCTGCTGCTAAACTCATGGCACAGAGACTAATGATC
ACCGACGTTCGTCTCTGCAGATTTCGTGGCATGGATGTGAACCAGCCGCCGCCTGCATGGATGGCATAGCT
ACG (SEQ ID NO: 7)

FIG. 6B

GAGGTCGGAGGTCGGAGATGGGTCGCGGCAAGGTGGTGCTGCAGCGGATCGAGAACAAGATCAGCCGCCAG
GTGACGTTCGCCAAGCGCCGCAACGGCCTGCTCAAGAAGGCCTACGAGCTCTCCCTCCTCTGCGACGCCGA
GGTCGCGCTCGTCCTCTTCTCCCACGCTGGCCGCCTCTACCAGTTCTCCTCCTCCTCCAAGTAATTACTCC
TTCCGATCTCCCCCAGTGCCGTACCATATCGATCCCTCCATTTCCTTTTCTCTTTGTGGTTTTGCCGAGTC
GATCCTTTTGATTTGCTCTCCCCGTTCAAACATTTTGTCCATACGCGACGTTCGATCTGAATTTTCTTGCG
TCTTAGGGCGTCCGTGCATGAACTTATGGGGGGCTGGGTCCGTACGTTCTTTCCCTCTTGTTTGCTGTTCT
GTTGGCCACTGTGTCAAAAGAGGCTAGCAAGAAACAAACAAAGGAAAAAGTGATGAGCTCACCCGCAGCAG
CAGATCGACGGACATACTATGCAGTAGGAGTATATGTCATGCGTATGTTTGTCTCATTCACGGTAGAGGAT
TAAAAAGGGGTTTTAATCTAAAAAAAACAAGAAGAAAAGATGTTTTTATTTGATGTACGCCTGACCACACC
TGTATTGAGGATACATGTATGCACATAATTAGAGCTTTGATCACCTGCTGAGATTAATTTGCACCAATATG
GCATGCATCCTTGTGAAACTCATACGGGCACTAATTGTTTTTCTACAAATTTTATCTAGCTTTGTCTTATG
GTCTGGGTAGTATGATGATCCACTTCTGAGAATTAATTTGAATTATGTAATTTTAAATACTTTTCTGCAGA
CCCAAGTTCAATCTATTTTTTTTCTCAAAACAAAGGTTCAGTCTAATTTGACACCTTTAAGGCGTAGGATT
GAATTATATATGCTTGTTTAATGTTATTTGTCAAAGAACTAAGAAAGGATATATACCGCTTTGAGTTAACT

FIG. 6B (con't)

GAATTGCATTAATTTTCTAGTCAAAGTACCGAAATAATACTATTGAACAAAATGAAACAGTTAAGTGCTTT
AATTCAACTGTGGCCTTACATGATGTGACAGGGCAAGTGCTGCATCATATGTACTAGGTACAAATGAAGTG
CTATTTGTACTTCCTTGGAGCAAAAGAAAACAAGTAATAAACTAGCTAATGTTAGGTTCGTACCTACTCCC
TCCGTCCCATAATGTAAGACCTTTTTTAACACGGTCTTATATTATGGGATGAAAGGAGTACGCAATAATTT
AAGCAGCTCTATAGGGTAGCATTACCTAATGATATCAGAACTTTATGTATGTTCGAGTCAAATATAGCTAG
GTTTTAATCTGTCAAAATTATAAAGCCACTGAGTTTGCTCAAAAAGTTTGTAAAAGCGCTGATACATGAAA
TGTGAAACCAGACTTGGTAAAATTGCATGCTAATATTTTGTAGGGCCAATCATGATTACTACTTGTCAGTT
CTATACAAACATGCCACTGGTGGCTAGCTTAAACTTTGTAGCAATTTTGGCTGAAATAGCTTTTTTGGTGA
AAATTAACAACTGTACTTCTCACAGTAGTAGCTCAATAAACATTCTTACAGTGGCATAGTTCTCCCAAAAG
TTTAATTAGTCAAAGGAAACAGATATGTCTTCTTTTTTATATAATGGAAAGTTCTTTTTAGGTACATCGTC
AAGTCTTCACTAGATTGTGATGTTTACACAACTTTGAAGCCATGTGTCAATGGCTATAAAGTGACCAAAAA
TTAGCTCATAAGACTAAGACAACATATAGAATTTGTTAGAAGTTGAACATACAGAAAGTTTATTATGCGAG
AGACCTTCATTGTCCAATAATTATCGAATTCTGTCATGTAAATAGTGATACTTAGTTTCTAATCCCTCCCC
CTCCCCAGTGAATCTGAATTTATGTTATTTACCTATGCGTGTACTTGCACAACTTAATCTCGAATTTTCAA
CTCATCGCAGCATGCTTAAGACCCTCGAGAAGTACCAGAGGTACATTTTCGCTTCCCAAGATGCTGCCGTG
CCGACTACCGATGAGATGCAGGTCTGAGGCTTTTATTCCCAATGCGCATATTATGAAGATTCTACAAATTT
TCCTCAGATACAACATCTTTGAATTTTTAACTAGCAGGTTATCAGAGAAATTTGTTTTCCTTCGTAGAACA
ATGTATCTATAATGCCCTAAATAACATATATAAATTGATTTTTGTGAAGAGATAAAACATTCAGTCATACA
TTTAAAATATTTCATTCTGTATGACGTACGTTATATGAAGCATTGCCTATTCGTAAATGTTACCTAGTTCA
CACATGATTGCTAAAAGGTATTTCTCTGCTGGTAAAGGTGTTATATTTCCGTGTTTAGAACATGGATTTCT
GTTGCTTGTCATATAGGCAGTGAACTAATTATTTTGTTTGACTTTTTTATGTAAAATTACTGCCTTGTAAA
CATGCCCACATGGTTTGAAGCAAAAGATAAACCTTTGATAAATTTTTAGCAGTTACAAAATATTAAATGGG
AATGTAAGTTCATGGCAATTAGAATGTTGGAAAGTACAGCTAGAGCATTGGCCCAGTGCATTTCATGCATA
CGCGCAGCATAATTCACGTACGTGGCTATCTATGTGAAATACAGCATCGAGTAACTGGGCACTGGGGAGAC
CTATATCTGCGCATGTTCCTTGAATTATCGCTAATGTACATGCATTTTGTGGTTGGTTATAACTTATAAGT
AGACTAACAGCTTGGTTGGCCACCACATGCAGTATTGTAGCAGATAGCAGCTTCAGACTGATTGGCCATAT
GCCATATACCTGCTGATGAGTTTATTACAACAGTGGAATGTATTAAAATTGATAAATACAATATGGCTATA
TGTTATATGGTATAAATGTGGTAGTTGTTTATTAAAAAGGCATGGGGTAAAATGTTCAATTTATGTTTAGT
AGAGCCTAAGCTATGGTACGCCTTCTTCATGGTCACGGTCATATTTTCCAAATGACATGTCCAAAAGAATA
GATTTGGACTTACTAGATCCTTTACTATTCATGCGAGAATTTATTGTTTACGAGGATTCACACACAGAGAG
TTGCCAGTATGTAATTTTTAGGATTCATGGTACAATTTAATCATAATCTTAATTGCTAGAACGTGTACTAA
TTTCTTTAGAAGATGGCAAGTGGGAACCTATAAACACACGAAGCAAGAACCATATGAACTCAACACAAGCA
ATCAACTAAGCCATAGCAAAGCGCAAACAAGAGAACATTGATAGATGATTGGTTTCCCTAACGCTAGATCG
TAGTGTAGATGAACAATCCAAGTGCTAGAAGTTGCGAGAGAGTGACAATATGACTCGTTTGATCTCTTGAT
GTTGTGTAGAAAGGGAGCCGCAGTTGGGTTCATCTTCTTTTTTCCGATAAACTTGGGTTCATCTTCATGGT
CATGATTATGGCATGCTCATGTCAAACCTTATGACATATAGTAAAACAAAGGTCTTCTGCGCACAATAAGG
ATATCGAAGTATAACAAAAGGTTCACATGAATTGCTCTAGGATTTTTCAGTGATGTGGTACTCCAAGTTTT
TATTCTAGGAAGTATTCCTAGATTTATGGTATAAGTTGGTATATATTAACTCTTCAGTCATAATCATCTCC
AAGGTGATACTTTGACCATTTGTTTTTTTTCTTCTTTTTGCGACTGAACTATCAATTTCTATAAAAAAATAT
GTTGATACACATAAAACATTTTACTCATTATGGAATTATGTTCTGCGATAATTCAAATATCTGTGTCAAAT
GTTTGTAATTTTATTTTTATTTTTACTGATAATCAGATTAAGAGTGCTTGCTGTTTTTTTTTTTGAAATGA
CCTATACTATGTGACTCATATGAAGGGGTACTCCTAGCTTGTAATCTTACAAAGTCGTCCGGGATTTATGT
TTAAAATTTTTAAATATTACCTCTTGTGTCATAATGTAGGTTGTCTCCAGCACGTGATACTTTGACAATCA
GTTTCCATAACAATATGCTGGTTCAAATGAAACATGGTACACTTTATAGATTATGTTTCACGACAACGTAA
ATTTTGTTTCACGTTTTGTAAGTTTCTTTTTTTTTATGATGAAACCAAGAATGTTTGACGGACACAACTTT
GGAATTGTCCTACAATGTTACTCACATGAAGTATTTGATTTTTGCGGGACAAAAAGGCATTTTTCTTAAGC
TTTTATTTTTGCAGGACAAAATGGCATTTTTCTTAAGTTTACTTGATTTAGCATTTTCCCCATATCTCCTT
CTTTACACTAACTGCAGAATACACTAACTGCAGAACAACTATCTGGAGTATATGGAGCTGAAGGCAAGAGT
TGAGGTTTTACAACGCTCACAAAGGTGATGTTTCTATATTCCTCTCAGATAATTGCTCATTAATTTCAGCA

FIG. 6B (con't)

GGTTACCGCAACATTTGCTATGTTTGCTAAAGTAAGTACTGTTGATGGTGCCACAGGAATCTCCTAGGCGA
GGATTTGGCTCCACTGAGTACAATCGAGCTTGAACAGCTTGAGGGTCAAGTAGGCAAGACCTTGAGGCAAA
TAAGGTCAAGAAAGGTAAACTACATAGCAATAAAAAAAGTTAAGAGTATAAGTAGAAATTAGGTTAATCTG
CTAAAATCCATTCGTCTTATCGAGCAACGCTTGCTGCTAGTTTCACTAACTAGTGTCCATGATTTAACCTG
TACCACAGACTCAAGTACTGCTGGATGAAATGTGCGACCTGAAGAGAAAGGTAGCACTAAAAATACTTTCC
ATTTCTGTTGCTAAATGATGGACGATGTCCTATTCCGTAGCTTCAAGCACAATCTTGTTTTGCAGGAGCAA
ATATTGCAGGATGCAAATATGACCCTGAAAAGAAAGGTAACATGACCCAAATCATTTTTCCTAGCTAGAAA
GGTCTGCATTTGTACGCACGTAGCTAGGGAGGGACCATCCTCAAGGAGAAGCTGTCTCATTTCACTTGGGC
CAGTGACAAGTGATTGGAAAGTTGATGACTCGGCAAGCCCACTAGTAGTTAGTTAGTAGGCAGGGGACCCC
TGGTTGGCACCACAGTATAAACACAGGTGGCTTTCAGGTACCACCAATTGCAGCTACCTGCCGTGTTTATG
TGTGTTTGTGCACTGCAAGCATTCTTCTTCTTCCTGGCTTTCAGAAAATCACTCTTCTTGTTTTTACCCTC
TACTGAAAACGGCTTCATCCATTGGTGTATGTAATGCTCTTGATCACTCCCGTTTCACTTCAGCTGGGCGA
GATCGAGCTGGAGGCGACACCTGATCCCCCGCAGCAGCCGCAGCAGCAGCAGATGTGGCAGGGCGACCGGG
GCGTGCCGCCCCACACGCCTCCGCAGCCAGAGCACTTCTTCCAGGCCCTAGAACGCTATCCTTCCCTGCAG
CCAGTGTAAGACTTCTAACTCTTTTTTTCCTTTTCCTGCTGCTAAACTCATGGCACAGAGACTAATGATCA
CCGACGTTCGTCTCTGCAGATTTCGTGGCATGGATGTGAACCAGCCGCCGCCTGCATGGATGGCATAGCTA
CG (SEQ ID NO: 8)

FIG. 7A

GAAAGGAAAAATTCTGCTCGTTTTTTTGCTCTGTGGTGTGTGTTTGTGGCGAGAGAAAATGATTTGGGGAA
AGCAAAATCCGGAGATTCGCACGTACGATCGTTCGACACGTCGACGCCCGGCGGGCCCGGGGTGGGGCATC
GTGTGGCTGCAGGACCGCGGGGCCCCGCAAAGCGGGCCGGGCCAATGGGTGCTCGACAGCGGCTATGCTCC
AGACCAGCCCGGTATTGCATACCGCGCTCGGGGCCAGATCCCTTTAAAAACCCCTCCCCCCCTGCCGGAAT
CCTCGTTTTGGCCTGGCCATCCTCCCTCTCCTCCCCTCTCTTCCACCTCACGTCCTCACCCAACCACCTGA
TAGCCATGGCTCCGCCGCCTCGCCTCCGCCTGCGCCAGTCGGAGTAGCCGTCGCGGTCTGCCGGTGTTGGA
GGGTAGGGGCGTAGGGTTGGCCCGGTTCTCGAGCGGAGATGGGGCGGGGGAAGGTGCAGCTGAAGCGGATC
GAGAACAAGATCAACCGGCAGGTGACCTTCTCCAAGCGCCGCTCGGGGCTTCTCAAGAAGGCGCACGAGAT
CTCCGTGCTCTGCGACGCCGAGGTCGGCCTCATCATCTTCTCCACCAAGGGAAAGCTCTACGAGTTCTCCA
CCGAGTCATGGTAAATTAAGCACGCGCTGTCTTTAAATTTGTTCCCCAATACGCCTTCGATTTCGATTTCC
TGCGCACCGTTCTGGTCCTGCGAGACGACCCGGCCGACCCCAGGGCCTTCTCCATTTCCGCGCTGCTGTTT
GGTAGATTCCGTTTGCCCGCTCGCTGTTTCCATCCGATTCTGCCGTGGCTGCTTGCTCGTTTTTCTTAGAA
TCGATGGGGGAGCTGGCGTTCCGCGCGGCCGCGATTTCTTGCTATGGGGGGTAGGGCGCGCGATGGGTCGC
CGGGCTATTTTATGCTCCGCCAGCGCCGGGAAGGTTGTTCATCTGGCGTATTTTGGGGAAATTTTGGTCCC
GGACGCGCCAGGTGGCACCCCAAGTGGAAGGGTTAAGACGGTAATCTCTTGATATTTCTATCGGGCTGGGG
TTATTTACGTAAAAAATATATATGGGGTTAAAGTGACATCGCAATTTAGCATGCTACCTCATCTTCTCATT
TGGAATCTTAACTAGACGCTACAATACCTTGTTGTCTCCCTCATCAAATCTGTGCTTGCTGCTTGAACAAA
TGAACCTCGTCATCTCGGTTATTTCCAGAATTTTGTTCCACAGGCTTTGCTATCATTCATATTGGTAGCTC
CGGCCATGCGGCCATTTTGTTGCTTGCTTGGAGATACTGTCTACGGCACGCACGGAGAAAAGAGTCACTTG
ACCAGCTAATGCATGGAATTATTGTCTGCAGCTGATGAAACTCCGGCATGAAGAGTCAAACCAAAAAGTAG
AGAGTTCCTTCCAAATATAAAATAAGAGTTTCTGCATACTTTTTTTCCCTTTCAACCATCATAGTTTGCCC
GTGATATTTGTTGGTGCTGGCGATGGTTCTTCACAAAGTAAAGGAGTCAATAAAATCACGGAGACTGATCC
ATTATTTCCCCCACACGCTGACATTAGTCCATGTTAGTTTCCCATTTCTGTCTGCTTCCATAATTCCCGTC
CGGCGAAGTACTAGATCAGCCTCCACGGTTTGAAAGTAAGATATATCATACCGTCGAAAGGATCGCTACTG
CTTAGTAAATATCCATTGTTGTTTGTAATCTTGCTGAGAAAGCAACATTACCATCAGCTTCATGGCAAGGA
CCTGTATGTTGAGGTGCTAAATCTCTTCTAGTTTTGTACCACTGAGGGTATGCGCGGCGCTAACGGAAAAG
GGTAGGTAAAGTTTTATTGGCTTGCCTTCAGCTTCCTTGGTTGTTTGACGCATAGGTGCTTGCATGCATGT
ATCAAGCTGGTCACGTGATGAAAACGCGTAAGAATCAAAGTCGGTTAAATTAAGATATAAATAGATGCAGT
CATATTTTAAGCTAGTGCTGCACTGTGAACTTCAGTATCTCAGATCAAAGTACTGAATAAAATTACCCCCT
GTTTCCGTGCTGTTCATTTGGAAAAGACTGCCATGAACATCCGAATTGGTAACCATGCATTAATCAGCTTG
CCGGCTTTATTTTCTTCTCTGTCGTTCCTTGTCATTTGGTTTGCTTTGCCTACCTCTGCACGATAGGCACG
TGTAAGTAGCTCACGGGGACAAGTAACTGCTATGCTTTGTCTAGAGCCTATGAGACAGCACGCTGATGCAC
CACGATATTCCATGGTTTAGGATCGGAACTAAAATCTTGAGATCTTACAATATTCTAAAAAGGCATCTATA
GCCTGCATATAACCGACTCAGGCACAAAATCAGCATTGATCGAGCAGGCATCATATGCATACACTAAAATG
CAGCTAATGATGTAGCCTGCTGATTTTCTGGACCTGGCTTGGATAATGGTTAATGTACCCAATTGTTATTC
ACTCTATATCCTCCATCTCCTTATCGGTCGATTAATTTACCACACATAGCAAAGGTCCAAAGCTGACATTG
CAACCAACTTTACTCATCTCTAGACTAGTAAACACGAAGTAAGCTGTTAGGGACTGTGTGATGGGTCTATG
TTACATGCATTTGTTGTCGGTCTAGTACTTAACCAAGTCTGGGAACCAGTTATCCTCTACACCTATTGTGT
CCCTAAACCTATATACTTGAGAGTAAAACAGAAGTTATTCCTAGGAATATCTGACTAAGCTATGGGATAGT
CAACTTCCATTTTTGCTCCTGCCACATCTTTACTTAGTCCACAAACGACATATAGATGATCAGCTAGAACC
GTTATTTAGAGTTTATATCTGCTCATTACATGTATTAATTCCATGAAATAGAAGAAAAACTGAATAGGCAC
ACAATATAGTTGAAGCTCGGCAGATGACTTCATAAGTGTCATATCTATTAACCATTTCACATATTGTTACA
TTTTTGCTGCAGTGATATTTTGTTAGCTCCCAGTTACAAGTTAACTAATATATGGAGATCCTGGGCACGTA
CATGTAAGCAGATCCTATCGACTTTCGCGTATCCGCTGATGGAATCACACCTCAGGATTTCATGGCATAGT
CTTGATATGTCACGAACTGGTTGTTACTTTATTTATTTATTTTACATTGTGTTTGCCCACCCAGATGATAG
AAATGTTATGTATTTAAAATGTAATCTCACAGTCATTGTTGTTGGTATCGACTGTATGCCAAAAAGGGTTT
TACCATGAAGTCTATTAATGAATAATTATTTATGTTACAACTTGATTGCTTTACATTAGTTAAAATTAGTT
ATTTTGTACCTTTGTGCCCCCCTTCTTGTTCAACCATTTATCTTACCAAACTATGCATCAACAAACATGCA
CAGTCACTATTCATAAATTTCATATTCTCAAAATTTAAATATTAAGAACAAAAGTTATGTTTCTACTTTTT

FIG. 7A (con't)

CCAACTGACAATTCTCTGAACTCAAATTTTATAATTTGAAATTTTAATATTAACATTTTATTTTAAAACTT
TTTGAATTTCTTTTTTATTATAAAAAAGTTTGGATGGCATAAATTTATGTATGAACTATTATGAAACCACA
AGCAATAACGAAAGTGTGTTTTTAAGCAAAACCTTATGACCCATCACTCAAATAGTTTGCGTTTGATTTTC
AAATTGACGCGCATTAAAGACATATACATGCAGTCTTCATATCACATGTGTGCTTTTCCTGCTTAAGGTAG
TAGGACTATCTCTTTTTTGAGAAACACCGATTACAACGTAGATGCACACACAAGTGCACATTACCACCACA
CGTACACACTCACACAATGTTTAGTAAGGACTAAAATTGTGGAGCTTCAAGATCTCTGGAACGTCAGGAAT
GTCGCCTCCCACGGAACGAATAATCCGCACAGTGTGTCAAACCATTGGTTCGATCTTCCTTGGTGGGCTGT
GAGTCAAGGTACTAAAAAAGCGGTAGGCGCTAATCTGAATTTTGCCTATGCCTAGTGCAATGACCGCCTAG
GCGCACTTATGCCTTCGTATGACAAAGAAGGAGATTTTACAACAATGAAATCAATGGTGCGGAGCCTAGAG
GGAGGTATCGGTGGTGAGTTGGAGTGAGAAATCCCTCCTCTGATTCAACCTTTCTTGACAACATAGCCCAA
ACAAGACCGTCCATTTTCTTTGCATCCCCCTTTTCCCGTCTCTTTGTATCGTTAGGTCTCTTTCATTCGTC
ATTTGTATGTAGCGATAATGGTGGTGTCTGCAGCTTCTTCCCTGCATTCGCTTCTCCTTTCCTACCGTCGC
CGGAAAAAGATCTCATCGGTCATGGAGAACATAGTCGGGCGCCTAAACCTTGGCCTATGGCAAAAGTGAGG
CGGTAGTCTGCTTAGCGCCTAAGTGGCTTCTTTTCATTGTCCTTTTTTCCATGTTGGGAGTACAACCGCAC
TCCTAACCCACTAATCATAGATTGGTTATCATCTAGTACTTTCTGTACCACTTTTATCTTACAAACGCGAG
GGTATTGTGGTGGAGAGCCATGTATTACAACTTTGATAATCAAAATTCAAAATTCAAGTCTCTGAAGATCC
TTTGAAAAATGTGTTTTGTCAAGGGCAAAAAATATATCTTTGTTTGCCATACCAAGATACTCCCTCCGTAA
AGAAATATAAGAGCGTTTAGGTCACTACTTGAGTGATCTGAACGCTCTTATATTTGTTTACCAGGGAGTAC
AAAAGACCATATTCTTGCACTAATTTTTACTAGTGGTTATGCCCGGGCATATGAGGGTCGGGAAGGAAGGC
GCAAGGGACATCTAGTAAAAATTAGTGAGAGAATAACCGCAAGGGACATTGTGCACTAATGTTTACCAGGG
AGTACAAAAGACCACATTGTGCCCGGGCATATGAGGGTCGGGAAGGAAGGCGCAAGGGACATCTATAAGAT
GGCTAAGATCGTGAGGAAGGCGAGGGATGTCAAACAAGTCAAATGCATCAAGGATAGAGCAGATCAACTCC
TGGTGAAGGACAAGGAGATCAAGCATAGATGACAGGAGTACTCCGACAAGCTATTCAATGGAGAGATGAAT
CTAGGGGTCTGAGATTAGGGAGGCTTTACAAAGAATAATGTTATAGGAGTCATTGGGCACCACTTAAGAGT
AATGGCAAGCGTGACCAAAAAATCAGTTTGTTTTCATGCCTGAGAGGTTGATCATGGAAGTCATTTTCTTGG
TATGAAAACTTATGGAGAAATACAGGGAGCAAAAAGAAGACTTGCATATGATGTTCATTGACTTGAAAAAG
TCCTGCAATAAGATACTGCAAAATGTCATGTGGTGGTCCTTGGAGAAACACAAAGTCCCAATAAAGTACAT
TACTCTCATCAAGGACATGTACAATGATCTCATGACAAGTGTTCAAAAAAGTGATGGCGACACTGATGACC
TTCCGCATAAAATAGGACAGCACCAAGGGTCAACTTCGAGCCCTTATCTTTTTGCCTTGATGATGGATGAG
GTCACAAGGGATATGCAAGGAGATATTCCATGGTGTATTCTCTTTACTATTGATGTGGTGCTAGTCAATGA
TAGTAGCTCGAGGCATAATGGAAAGTTAGAGCTATGGAGACAAACTTTGGATCAAAGTTTTTAGGCTTAGT
AGAACTAAAATTGAGTACATGAGGTGCGGTTTCAGTGCTACTTGGCACGAGGAGGTTAGCCTCAATGGGTA
GGTGGTACCTCAGAAGGGCACCTTTTGATATTTGGGATCAGTGTTGGAAAAGGATGCCGATATTGATGAAG
ATGTGAGCCATTAAATCAAAGTCGGATGGAGGAAATGATGCCAAGTTTCTGGTGTTCTCTCTTGACAAGAT
AGTGCCACGAAAGCTAAAAGGCAGGTTCGATAGGACGGCGCCCCGCAATGTATGGCGCTGAGTATTGGCCG
ACTAAAATGAGACATATTCAACAATTGGGTGTAGCAGAAATGCGCATCTTGAGATGGATGTGTGGTCACCC
AAGAAAGGATCGAGTCCAAAATGATGATATACATGTAGAGTCGGGGTAGCACCGATTGAAGGGAAGCTTGT
CGAACATCGTCTGAGATGGCTTGGATATATACAAAGTAGGCCTTTAGAAACTTTCGTGCATAGCAGGCGGT
TAATACATGCTAATAATGTAAGAGAGGTTGGGCTAGACCAAACTTGACATGGAAGGAGTCCGTGAAGAGAG
ATCTGAAGCACTAAAGTATCACACGGAACTAGTCATGGACAGGGGTGTGTGGAAGTTAGCTATCCACACGC
CAGAACCATTACTTGGTTTTGAGATCTTATGGATTTCAGCTCTACCCTATCCAACTTATTTGGGACTAAAC
GCTTTGTTGTTGTATCTCTTGCCTTGGTCTTAGCAACTTACCATGTGCATGTCTTTTCTCAAAAAGGAAAA
TTGAATGCCAAGTATTTCCTGAAGTTGTACATTGTACAATTTGATGTCCTTGCTCCACGGTACATCAGATT
TCCCATCTCATGATGATGCAACAACTAGGTCTTAGAGCAACTCTAGCAGAGTCTTCATGGCTTCCGTCGCT
ATATTTCTTTTATCTCGCTCCATACACAGGTCTCGTGGCCTCCATATTTGGAGGTTGGAGAGGTCCAGTAA
GGAGCTCGCCCCAAAACCAACCGCTAAAGTTTTAAGCTTCCTCCTCGCGCCTCCTGTCGGATTTGAAGCAA
CCCGCGCCCTCGGATTCTTATGGCGGTCCATTGGATGACCGCCATGCGGCATCATCTTCTTGCTTGCATGT
GAGCAGACTGGAGGTGTGCGAGTAGGTCGCTGCAGCATTTCTCATAGGGAGGCGCGCCCTTCGACTACCCG
CCATTAGCTGCCACCCGCGTCCCCAAGTGCCTCCCTAATGGCGCCTGCGGTGGCCTGTAAAAGGCCGGCGC
CCTCCGCTCTCTAGCTTCAATGCTATCTTCGACGCCTCTTATTCCAATCTCACACGCCTCCAATCCACCAT
CCCCTTTGTCGTCCACAGCGCATCCAGAGGAGCTCCCTCTCGCCTTCAATTTTTGGCATAAGGTGGAGGAG

FIG. 7A (con't)

TAGCCCGCGGATCCTTTGCCCCCCTTTAGGGACCAGACGGACCTAGTCCTGGAGGGGGGCTGCGCAGAGCA
ACTTGTAGCACCCAAGATTCTATCCCGATCACGTGATGAATTCATGATCGGAGCAGAATCGCATTTCGAGC
GCATAGCGAGGTGGATATCATTACAACATACCATGCACTAAATAGATGAGAATACCAGATAAAGGTTTACA
CTCGCCACAAGCTACAACATGAATACATCAATACACAACAATCATCATACAGGAGAGCAGGATCCGACTAT
GGATGAAATCAAACAAAAAGAAGAACGACATCTACCCTGCTAATCCCGGGCTCCTGAACTGGAACCCATCC
TATGATCGACGAAGAAGCAGAAGAAGAACTCCAAAAGCAAACATGCATCGCTCTCACGTCAAGCATTGCTT
TATCTATACCTGCACCTGTTGTAGTAATCTATGAGCCATGGGGACCcAGCAATCTCATTACCAAGGGTAGC
AAAACTAGCAAAGATTAATGGGTATGGAAGGGTTAAGTGGTGAGGAGGCTGGAAGCATTAAGCATTTGTAT
GGTGGCTAACTTACGAGTACAAGAGTAAGAAGAGTAAACTACACATAGCGGTCGCAAACTATTAATGATCA
AGAAGTGATCCTGAACTACTTATGAGTCAGTCATAACCCCACCGTGTTCACTTCCCGAACTCCTTGGAAAA
GAGACGATCACGTAACGCACGCGGTTGGTGTATTTTAATTGGGTTCAGTGTCAAGTTCTCTAAAATCGGAT
ATTATAAATTTTTAAGTCGCCACATAACCGCGGGCACGGCTTCCGAAAAGATTTAGCCCTGCAGGGGTGCA
CCAAGTAGTCCATTATAAATTACCACATGCATCCGATGGAACATCCTCACACCATGATAACACGATGCTTA
CAATAAGGAACCCCGGTGGACAAGCCACTCGTCAAAGGCAAAACTAAACCAGCAAGACCACCCGGTGTGTC
GTCACCCCGATAAGAGCCGCGCCTATTTTCTAGGGTTGCCTAACCCTTGGGATCCCTTGGACCACCTTACT
ATGTGCATGTTTTCTTTTCACACGGGCATTTATCTGCTTTGGCATCAAAGCTTTCATTTGAAAATTTGCTA
CTACCACCTATATTTGTACTGACAATACCTTTGCATGGACCCACACATTAGGTTTTAAAATGGTTCTCACA
TTCGTGTTGTCTTACTTATCTAGGCATGGCTCTTGCCCAGATAATTGTTGTTGGTCACACCCTTCTATATT
ATCGGTTTGTGAGTCTAGCTGATTGGATACGTGAGTTGTTGCACACTCTTGAACTGATTTTGACTTGATGA
CCATTGTAACCATTTGCGGGTTATAGGCTAGCACATAGTTCAACACTATAACTAATTGTTGGTTCATTCCT
ACTATAGGTTATAGGGTAGCGTTTGACAATTTTCCATGTGTTGTGGGTACTTGTGACAATTGAGGACACGA
TGTTTGTGGTGACAGAGAACACGTTGACCTCCACAAATAGTTAGGATGCTGGGTAAAGCCTACGGGAAAAC
AGGGAGAAGGTATAGGAGGAGAATAACATGAGTAGTAAAAAAGTTAATGACTTAAATACAACATCAAGGAA
CGTTTCTTAAACTGAAGCTCTAGCACTATAGTTAAATAATTTGAATCTGGCAGAAATTATACTAACCTTGC
CTAGCACAATTCCACCCCTAAACTTCTGTTTTGCAAATTTCGTTAAGTCTATAGACAGAAGAAAAGGGTCA
CTCTATTTTCCCAACAAAACTTGAACAACACCAGAACCTTAATTTGAAGTCAGTTTCGTGCTCTTTCTATC
ATTTACACGTCACAGTGAAATGCTTTGCAAACTATTTGACCAGATGCTGTATACCACATTTGAATCTCATT
TGCATATACTGACATGAAACAACGCATTACAGAAAAGCTTCTGATATGTCAAAATGTATCATATATCAATT
CTTGAGATTGTGCATATACTGGACATTAATCTTGTTTACATGTACTTCCAATGACTAGATATTTCTTTCTC
TTATGCAGTATGGACAAAATTCTTGAACGGTATGAGCGCTATTCTTATGCAGAAAAGGTTCTCGTTTCAAG
TGAATCTGAAATTCAGGTAAAAATGAAAAACAAGCGGTTTGCTTTCCTTTAGCTATGAAATAAATTGTTGC
CGATATCAGATGTTCTGAAATTTATTTGTAGGCCACTATATTTTGAATGATTTCCATGCGCTATGAAGTTA
ATTGACTTGCAACTATGGATTGTTGGTCTATTTGATTCTCTTGTAACCTATTATCAGTTTTTCTTCGATGA
ATGCTTAGGCATGGTCGAATAATGTAACCAAATACCACTTGACCAATTTACTTTCATGGCTACTGAACTAG
ACTAGCGTGCTGATTCGTACATACTGCCTTTGGAAGAACTACAAAAATGTGATCTGACTTTAAGAGTTACT
AAATTAGTACGTAGTAAACTGCAATGCATGGCCAGATCAGCAATTCTGGATTAGCCGGCTGAGTTTTTGAA
GGGCTTAGCAACAAAAATTGACAAGCTTATATATTATAATGGCTTTAAAATACTTGTGTGCATCAGTGAAA
ATCACAATATTTTGATTGCAATAACAAAATGCTATCCTAGATTATTAAGACTTGTTACTAGATTGGTCATT
GATCTTAAGTTCTTAGGATAAACTGTTGAATCTCCAGTCCTTCGGATTGTATTATGCTACTAATGGCCATT
AAGGATAGCCCCATGACATTAGTTCTCATCTCCAATTTTTCTGTATTGTTTGCGATATTGCTGCAGTTTCT
TATTACAGCTTGTCTAAGGCTAACCATCTAGGATAAAAAGTAGATCCTGCAGACTTAGAAGATCCAGTTAG
GCTCAATATTCTTATTTTTGTAACTCGGAACTCCAGGACCTCGCTTCAATTTTTTGGCCAATTTTTGCACA
AACCAAGTTGTAGCTCCAACTGAGGGATCCAACCAGTTCTATCTGATTGCTGACAAACAGATTCAGCATGT
ACGTATGACGAGGACTATTTAAACATGTAATTACTAACCCAAAAAATATTCCAAATTTTATTTAAATATTT
ACCTCCGCTGCAGCATTTTTAATATTACGAAATATGATTTTTACATCTGATAGTAACACTTGTTGCAGTGA
CATAATTGATTTGAAGTTATGAAAATTCAAGTTCACTGCACAGAACAATCCTTCCTGATTTATGCCCCCGG
GGTAAAGGAGGAGGGTTGTGATAGGCTTGGCGAGCCAACGTAAAAACTCAGCCACTCTTATGGAGATGAAA
CCCAAAAGCCAAAGAGCTAGCTATGGACAGGGGTGCGTGGAAGCTTGCTATCCATGTGCCAGAGCCATGAG
TTGGTTGCGAGATCTTATGGGTTTCACCTCTAGCCTACCCCAACTTGTTTGGGACTAAAGGCTTTGTTGTT
GTTGTTGGTGGTGGTGGTGTCAATGTTGTTAAAGTCTCTTTGTTCATTTCTGAACTAACTTAGCCTATTTG
TAGCATTTCTGTCATTGTTCCTTCCTGTCCCACCCAAAGTTAGCAATGCGATTGTTATTTGTTTGTGCAGG
GAAACTGGTGTCACGAATATAGGAAACTGAAGGCGAAGGTTGAGACAATACAGAAATGTCAAAAGTAATTT

FIG. 7A (con't)

GTAACGATTTTGGTTGATTGCCAGTATATTGTATACACTCTGAAGATAAATGGGACTGAATTTCTACATCC
TGCATCTGCAGGCATCTCATGGGAGAGGATCTTGAATCTTTGAATCTCAAGGAGTTGCAGCAACTGGAGCA
GCAGCTGGAAAGCTCACTGAAACATATCAGATCCAGGAAGGTACTGATTTAAATGATTTGATACAGCAGCA
CAATATATAAAAAAACAAGAAAAACACTTGCAGAGAAGTTCAGCAAAGTATATCTGAAATCAGATTCTAGA
CTGAGATGTTCAAAATATGTATATGCATTTTAGTCATATGCTCTTCATAGTTAAAAAAATGACTAATTTTT
TTCATTTTTTGTACTTGCAGAACCAACTTATGCACGAATCCATTTCTGAGCTTCAGAAGAAGGTAAGCTGT
CAACCTTGCATACCTTATTCGGTATTCGAACTGGTCAACTTGTCATGAAGCCTTAGCTTGTTTCAAGATTT
GTGACATTATAACATGTATGCAAGTAACTGGTCTACATGCACGTAACCTCATTACATCGTTCTTGCTGCAG
GAGAGGTCACTGCAGGAGGAGAATAAAGTTCTCCAGAAGGAAGTAAGCCCGTTATATCACCTTATGGTCCA
ACCGGTCTAAATTGTTCCGTATAGCAAATTTTATTGACAGAGGTCCGTGTCCCTTCCCCACAGCTCGTGGA
GAAGCAGAAGGCCCATGCGGCGCAGCAAGATCAAACTCAGCCTCAAACCAGCTCTTCATCTTCTTCCTTCA
TGCTGAGGGATGCTCCCCCTGCCGCAAATACCAGGTGATGATGTACATCACAAGTCTAATCTTATTCAGAG
TTCAAGTAACCATCTTTTGAATTGGTCGGGTTGTTCCTTGCAGCCCACTTTTGGTCTCTATGCAGTTCTGT
CGGGCCACATTTAAGTAACATAATACTAATATGCTTGTGTTCGCTTTGGTTGTGCAGCATTCATCCAGCGG
CAACAGGCGAGAGGGCAGAGGATGCGGCAGTGCAGCCGCAGGCCCCACCCCGGACGGGGCTTCCACCGTGG
ATGGTGAGCCACATCAACGGGTGAAGGGCATCCAGCCCATACAGGCGTACTATTCAGTAGAGGGT
(SEQ ID NO: 9)

FIG. 7B

GAAAGGAAAAATTCTGCTCGTTTTTTTGCTCTGTGGTGTGTGTTTGTGGCGAGAGAAAATGATTTGGGGAA
AGCAAAATCCGGAGATTCGCACGTACGATCGTTCGACACGTCGACGCCCGGCGGGCCCGGGGTGGGGCATC
GTGTGGCTGCAGGACCGCGGGGCCCCGCAAAGCGGGCCGGGCCAATGGGTGCTCGACAGCGGCTATGCTCC
AGACCAGCCCGGTATTGCATACCGCGCTCGGGGCCAGATCCCTTTAAAAACCCCTCCCCCCCTGCCGGAAT
CCTCGTTTTGGCCTGGCCATCCTCCCTCTCCTCCCCTCTCTTCCACCTCACGTCCTCACCCAACCACCTGA
TAGCCATGGCTCCGCCGCCTCGCCTCCGCCTGCGCCAGTCGGAGTAGCCGTCGCGGTCTGCCGGTGTTGGA
GGGTAGGGGCGTAGGGTTGGCCCGGTTCTCGAGCGGAGATGGGGCGGGGGAAGGTGCAGCTGAAGCGGATC
GAGAACAAGATCAACCGGCAGGTGACCTTCTCCAAGCGCCGCTCGGGGCTTCTCAAGAAGGCGCACGAGAT
CTCCGTGCTCTGCGACGCCGAGGTCGGCCTCATCATCTTCTCCACCAAGGGAAAGCTCTACGAGTTCTCCA
CCGAGTCATGGTAAATTAAGCACGCGCTGTCTTTAAATTTGTTCCCCAATACGCCTTCGATTTCGATTTCC
TGCGCACCGTTCTGGTCCTGCGAGACGACCCGGCCGACCCCAGGGCCTTCTCCATTTCCGCGCTGCTGTTT
GGTAGATTCCGTTTGCCCGCTCGCTGTTTCCATCCGATTCTGCCGTGGCTGCTTGCTCGTTTTTCTTAGAA
TCGATGGGGGAGCTGGCGTTCCGCGCGGCCGCGATTTCTTGCTATGGGGGGTAGGGCGCGCGATGGGTCGC
CGGGCTATTTTATGCTCCGCCAGCGCCGGGAAGGTTGTTCATCTGGCGTATTTTGGGGAAATTTTGGTCCC
GGACGCGCCAGGTGGCACCCCAAGTGGAAGGGTTAAGACGGTAATCTCTTGATATTTCTATCGGGCTGGGG
TTATTTACGTAAAAAATATATATGGGGTTAAAGTGACATCGCAATTTAGCATGCTACCTCATCTTCTCATT
TGGAATCTTAACTAGACGCTACAATACCTTGTTGTCTCCCTCATCAAATCTGTGCTTGCTGCTTGAACAAA
TGAACCTCGTCATCTCGGTTATTTCCAGAATTTTGTTCCACAGGCTTTGCTATCATTCATATTGGTAGCTC
CGGCCATGCGGCCATTTTGTTGCTTGCTTGGAGATACTGTCTACGGCACGCACGGAGAAAAGAGTCACTTG
ACCAGCTAATGCATGGAATTATTGTCTGCAGCTGATGAAACTCCGGCATGAAGAGTCAAACCAAAAAGTAG
AGAGTTCCTTCCAAATATAAAATAAGAGTTTCTGCATACTTTTTTTCCCTTTCAACCATCATAGTTTGCCC
GTGATATTTGTTGGTGCTGGCGATGGTTCTTCACAAAGTAAAGGAGTCAATAAAATCACGGAGACTGATCC
ATATTTCCCCCACACGCTGACATTAGTCCATGTTAGTTTCCCATTTCTGTCTGCTTCCATAATTCCCGTCC
GGCGAAGTACTAGATCAGCCTCCACGGTTTGAAAGTAAGAAATATCATACCGTCGAAAGGATCGCTACTGC
TTAGTAAATATCCATTGTTGTTTGTAATCTTGCTGAGAAAGCAACATTACCATCAGCTTCATGGCAAGGAC
CTGTATGTTGAGGTGCTAAATCTCTTCTAGTTTTGTACCACTGAGGGTATGCGCGGCGCTAACGGAAAAGG
GTAAGTAAAGTTTTATTGGCTTGCCTTCAGCTTCCTTGGTTGTTTGACGCATAGGTGCTTGCATGCATGTA
TCAAGCTGGTCACGTGATGAAAACGCGTAAGAATCAAAGTCGGTTAAATTAAGATATAAATAGATGCAGTC
ATATTTTAAGCTAGTGCTGCACTGTGAACTTCAGTATCTCAGATCAAAGTACTGAATAAAATTACCCCCTG
TTTCCGTGCTGTTCATTTGGAAAAGACTGCCATGAACATCCGAATTGGTAACCATGCATTAATCAGCTTGC
CGGCTTTATTTTCTTCTCTGTCGTTCCTTGTCATTTGGTTTGCTTTGCCTACCTCTGCACGATAGGCACGT
GTAAGTAGCTCACGGGGACAAGTAACTGCTATGCTTTGTCTAGAGCCTATGAGACAGCACGCTGATGCACC

FIG. 7B (con't)

ACGATATTCCATGGTTTAGGATCGGAACTAAAATCTTGAGATCTTACAATATTCTAAAAAGGCATCTATAG
CCTGCATATAACCGACTCAGGCACAAAATCAGCATTGATCGAGCAGGCATCATATGCATACACTAAAATGC
AGCTAATGATGTAGCCTGCTGATTTCTGGACCTGGCTTGGATAATGGTTAATGTACCCAATTGTTATTCA
CTCTATATCCTCCATCTCCTTATCGGTCGATTAATTTACCACACATAGCAAAGGTCCAAAGCTGACATTGC
AACCAACTTTACTCATCTCTAGACTAGTAAACACGAAGTAAGCTGTTAGGGACTGTGTGATGGGTCTATGT
TACATGCATTTGTTGTCGGTCTAGTACTTAACCAAGTCTGGGAACCAGTTATCCTCTACACCTATTGTGTC
CCTAAACCTATATACTTGAGAGTAAAACAGAAGTTATTCCTAGGAATATCTGACTAAGCTATGGGATAGTC
AACTTCCATTTTTGCTCCTGCCACATCTTTACTTAGTCCACAAACGACATATAGATGATCAGCTAGAACCG
TTATTTAGAGTTTATATCTGCTCATTACATGTATTAATTCCATGAAATAGAAGAAAAACTGAATAGGCACA
CAATATAGTTGAAGCTCGGCAGATGACTTCATAAGTGTCATATCTATTAACCATTTGACATATTGTTACAT
TTTTGCTGCAGTGATATTTTGTTAGCTCCCAGTTACAAGTTAACTAATATATGGAGATCCTGGGCACGTAC
ATGTAAGCAGATCCTATCGACTTTCGTGGATCCGCTGATGGAATCACACCTCAGGATTTCATGGCATAGTC
TTGATATGTCACGAACTGGTTGTTACTTTATTTATTTATTTTACATTGTGTTTGCCCACCCAGATGATAGA
AATGTTATGTATTTAAAATATAATCTCACAGTCATTGTTGTTGGTATGGACCGTATGCCAAAAAGGGTTTT
ACCATGAAGTCTATTAATGAATAATTATTTATGTTACAACTTGATTGCTTTACATTAGTTAAAATTAGTTA
TTTTGTACCTTTGTGCCCCCCTTCTTGTTCAACCATTTATCTTACCAAACTATGCATCAACAAACATGCAC
AGTCACTATTCATAAATTTCATATTCTCAAAATTTAAATATTAAGAACAAAAGTTATGTTTCTACTTTTTC
CAACTGACAATTCTCTGAACTCAAATTTTATAATTTGAAATTTTAATATTAACATTTTATTTTAAAACTTT
TTGAATTTCTTTTTTATTATAAAAAAGTTTGGATGGCATAAATTTATGTATGAACTATTATGAAACCACAA
GCAATAACGAAAGTGTGTTTTTAAGCAAAACCTTATGACCCATCACTCAAATAGTTTGCGTTTGATTTTCA
AATTGACGCGCATTAAAGACATATACATGCAGTCTTCATATCACATGTGTGCTTTTCCTGCTTAAGGTAGT
AGGACTATCTCTTTTTTGAGAAACACCGATTACAACGTAGATGCACACACAAGTGCACATTACCACCACAC
GTACACACTCACACAATGTTTAGTAAGGACTAAAATTGTGGAGCTTCAAGATCTCTGGAACGTCAGGAATG
TCGCCTCCCACGGAACGAATAATCCGCACAGTGTGTCAAACCATTGGTTCGATCTTCCTTGGTGGGCTGTG
AGTCAAGGTACTAAAAAAGCGGTAGGCGCTAATCTGAATTTTGCCTATGCCTAGTGCAATGACCGCCTAGG
CGCACTTATGCCTTCGTATGACAAAGAAGGAGATTTTACAACAATGAAATCAATGGTGCGGAGCCTAGAGG
GAGGTATCGGTGGTGAGTTGGAGTGAGAAATCCCTCCTCTGATTCAACCTTTCTTGACAACATAGCCCAAA
CAAGACCGTCCATTTTCTTTGCATCCCCCTTTTCCCGTCTCTTTGTATCGTTAGGTCTCTTTCATTCGTCA
TTTGTATGTAGCGATAATGGTGGTGTCTGCAGCTTCTTCCCTGCATTCGCTTCTCCTTTCCTACCGTCGCC
GGAAAAAGATCTCATCGGTCATGGAGAACATAGTCGGGCGCCTAAACCTTGGCCTATGGCAAAAGTGAGGC
GGTAGTCTGCTTAGCGCCTAAGTGGCTCCTTTTCATTGTCCTTTTTTCCATGTTGGGAGTACAACCGCACT
CCTAACCCACTAACCATAGATTGGTTATCATCTAGTACTTTCTGTACCACGTTTATCTTACAAACGCGAGG
GTATTGTGGTGGAGAGCCATGTATTACAACTTTGATAATCAAAATTCAAAATTCAAGTCTCTGAAGATCCT
TTGAAAAATGTGTTTTGTCAAGGGCAAAAAATATATCTTTGTTTGCCATACCAAGATACTCCCTCCGTAAA
GAAATATAAGAGCGTTTAGGTCACTACTTGAGTGATCTGAACGCTCTTATATTTGTTTACCAGGGAGTACA
AAAGACCATATTCTTGCACTAATTTTTACTAGTGGTTATGCCCGGGCATATGAGGGTCGGGAAGGAAGGCG
CAAGGGACATCTAGTAAAAATTAGTGAGAGAATAACCGCAAGGGACATTGTGCACTAATGTTTACCAGGGA
GTACAAAAGACCACATTGTGCCCGGGCATATGAGGGTCGGGAAGGAAGGCGCAAGGGACATCTATAAGATG
GCTAAGATCGTGAGGAAGGCGAGGGATGTCAAACAAGTCAAATGCATCAAGGATAGAGCAGATCAACTCCT
GGTGAAGGACAATGAGATCAAGCATAGATGACAGGAGTACTCCGACAAGCTATTCAATGGAGAGATGAATC
TAGGGGTCTGAGATTAGGGAGGCTTTACAAAGAATAATGTTATAGGAGTCATTGGGCACCACTTAAGAGTA
ATGGCAAGCGTGACCAAAAATCAGTTTGTTTTCATGCCTGAGAGGTTGATCATGGAAGTCATTTTCTTGGT
ATGAAAACTTATGGAGAAATACAGGGAGCAAAAAGAAGACTTGCATATGATGTTCATTGACTTGAAAAAGT
CCTGCAATAAGATACTGCAAAATGTCATGTGGTGGTCCTTGGAGAAACACAAAGTCCCAATAAAGTACATT
ACTCTCATCAAGGACATGTACGATGATCTCATGACAAGTGTTCAAAAAAGTGATGGCGACACTGATGACCT
TCCGCATAAAATAGGACAGCACCAAGGGTCAACTTCGAGCCCTTATCTTTTTGCCTTGATGATGGATGAGG
TCACAAGGGATATGCAAGGAGATATTCCATGGTGTATTCTCTTTACGATTGATGTGGTGCTAGTCAATGAT
AGTAGCTCGAGGCATAATGGAAAGTTAGAGCTATGGAGACAAACTTTGGATCAAAGTTTTTAGGCTTAGTA
GAACTAAAATTGAGTACATGAGGTGCGGTTTGAGTACTACTTGGCACGAGGAGGTTAGCCTCAATGGGTAG
GTGGTACCTCAGAAGGGCACCTTTTGATATTTGGGATCAGTGTTGGAAAAGGATGCCGATATTGATGAAGA

FIG. 7B (con't)

TGTGAGCCATTAAATCAAAGTCGGATGGAGGAAATGATGCCAAGTTTCTGGTGTTCTCTCTTGACAAGATA
GTGCCACGAAAGCTAAAAGGCAGGTTCGATAGGACGGCGCCCCGCAATGTTTGGCGCTGAGTATTGGCCGA
CTAAAATGAGACATATTCAACAATTGGGTGTAGCAGAAATGCGCATCTTGAGATGGATGTGTGGTCACCCA
AGAAAGGATCGAGTCCAAAATGATGATATACATGTAGAGTCGGGGTAGCACCGATTGAAGGGAAGCTTGTC
GAACATCGTCTGAGATGGCTTGGATATATACAAAGTAGGCCTTTAGAAACTTTCGTGCATAGCAGGCGGTT
AATACATGCTAATAATGTAAGAGAGGTTGGGCTAGACCAAACTTGACATGGAAGGAGTCCGTGAAGAGAGA
TCTGAAGCACTAAAGTATCACACGGAACTAGTCATGGACAGGGGTGTGTGGAAGTTAGCTATCCACACGCC
AGAACCATTACTTGGTTTTGAGATCTTATGGATTTCAGCTCTACCCTATCCAACTTATTTGGGACTAAACG
CTTTGTTGTTGTATCTCTTGCCTTGGTCTTAGCAACTTACCATGTGCATGTCTTTTCTCAAAAAGGAAAAT
TGAATGCCAAGTATTTCCTGAAGTTGTACATTGTACAATTTGATGTCCTTGCTCCACGGTACATCAGATTT
CCCATCTCATGATGATGCAACAACTAGGTCTTAGAGCAACTCTAGCAGAGTCTTCATGGCTTCCGTCGCTA
TATTTCTTTTATCTCGCTCCATACACAGGTCTCGTGGCCTCCATATTTGGAGGTTGGAGAGGTCCAGTAAG
GAGCTCGCCCCAAAACTAACCGCTAAAGTTTTAAGCTTCCTCCTCGCGCCTCCTGTCGGATTTGAAGCAAC
CCGCGCCCTCGGATTCCTATGGCGGTCCATTGGATGACCGCCATGCGGCATCATCTTCTTGCTTGCATGTG
AGCAGACTGGAGGTGTGCGAGTAGGTCGCTGCAGCATTTCTCATAGGGAGGCGCGCCCTTCGACTACCCGC
CATTAGCTGCCACCCGCGTCCCCAAGTGCCTCCCTAATGGCGCCTGCGGTGGCCTGTAAAAGGCCGGCGCC
CTCCGCTCTCTAGCTTCAATGCTATCTTCGACGCCTCTTATTCCAATCTCACACGCCTCCAATCCACCATC
CCCTTTGTCGTCCACAGCGCATCCAGAGGAGCTCCCTCTCGCCTTCAATTTTTGGCATAAGGTGGAGGAGT
AGCCCGCGGATCCTTTGCCCCCCTTTAGGGACCAGACGGACCTAGTCCTGGAGGGGGGCTGCGCAGAGCAA
CTTGTAGCACCCAAGATTCTATCCCGATCACGTGATGAATTCATGATCGGAGCAGAATCGCATTTCGAGCG
CATAGCGAGGTGGATATCATTACAACATACCATGCACTAAATAGATGAGAATACCAGATAAAGGTTTACAC
TCGCCACAAGCTACAACATGAATACATCAATACACAACAATCATCATACAGGAGAGCAGGATCCGACTATG
GATGAAATCAAACAAAAAGAAGAAAGACATCTACCCTGCTAATCCCGGGCTCCTGAACTGGAACCCATCCT
ATGATCGACGAAGAAGCAGAAGAAGAACTCCAAAAGCAAACATGCATCGCTCTCACGTCAAGCATTGCTTT
ATCTATACCTGCACCTGTTGTAGTAATCTATGAGCCATGGGGACCCAGCAATCTCATTACCAAGGGTAGCA
AAACTAGCAAAGATTAATGGGTATGGAAGGGTTAAGTGGTGAGGAGGCTGGAAGCATTAAGCATTTGTATG
GTGGCTAACTTACGAGTACAAGAGTAAGAAGAGTAAACTACACATAGCGGTCGCAAACTATTAATGATCAA
GAAGTGATCCTGAACTACTTATGAGTCAGTCATAACCCCACCGTGTTCACTTCCCGAACTCCTTGGAAAAG
AGACGATCACGTAACGCACGCGGTTGGTGTATTTTAATTGGGTTCAGTGTCAAGTTCTCTAAAATCGGATA
TTATAAATTTTTAAGTCGCCACATAACCGCGGGCACGGCTTCCGAAAAGATTTAGCCCTGCAGGGGTGCAC
CAAGTAGTCCATTATAAATTACCACATGCATCGGATGGAACATCCTCACACCATGATAACACGATGCTTAC
AATAAGGAACCCCGGTGGACAAGCCACTCGTCAAAGGCAAAACTAAACCAGCAAGACCACCCGGTGTGTCG
TCACCCCGATAAGAGCCGCGCCTATTTTCTAGGGTTGCCTAACCCTTGGGATCCCTTGGACCACCTTACTA
TGTGCATGTTTTCTTTTCACACGGGCATTTATCTGCTTTGGCATCAAAGCTTTCATTTGAAAATTTGCTAC
TACCACCTATATTTGTACTGACAATACCTTTGCATGGACCCACACATTAGGTTTTAAAATGGTTCTCACAT
TCGTGTTGTCTTACTTATCTAGGCATGGCTCTTGCCCAGATAATTGTTGTTGGTCACACCCTTCTATATTA
TCGGTTTGTGAGTCTAGCTGATTGGATACGTGAGTTGTTGCACACTCTTGAACTGATTTTGACTTGATGAC
CATTGTAACCATTTGCGGGTTATAGGCTAGCACATAGTTCAACACTATAACTAATTGTTGGTTCATTCCTA
CTATAGGTTATAGGGTAGCGTTTGACAATTTTCCATGTGTTGTGGGTACTTGTGACAATTGAGGACACGAT
GTTTGTGGTGACAGAGAACACGTTGACCTCCACAAATAGTTAGGATGCTGGGTAAAGCCTACGGGAAAACA
GGGAGAAGGTATAGGAGGAGAATAACATGAGTAGTAAAAAAGTTAATGACTTAAATACAACATCAAGGAAC
GTTTCTTAAACTGAAGCTCTAGCACTATAGTTAAATAATTTGAATCTGGCAGAAATTATACTAACCTTGCC
TAGCACAATTCCACCCCTAAACTTCTGTTTTGCAAATTTCGGTAAGTCTATAGACAGAAGAAAAGGGTCAC
TCTATTTTCCCAACAAAACTTGAACAACACCAGAACCTTAATTTGAAGTCAGTTTCGTGCTCTTTCTATCA
TTTACACGTCACAGTGAAATGCTTTGCAAACTATTTGACCAGATGCTGTATACCACATTTGAATCTCATTT
GCATATACTGACATGAAACAACGCATTACAGAAAAGCTTCTGATATGTCAAAATGTATCATATATCAATTC
TTGAGATTGTGCATATACTGGACATTAATCTTGTTTACATGTACTTCCAATGACTAGATATTTCTTTCTCT
TATGCAGTATGGACAAAATTCTTGAACGGTATGAGCGCTATTCTTATGCAGAAAAGGTTCTCGTTTCAAGT
GAATCTGAAATTCAGGTAAAAATGAAAAACAAGCGGTTTGCTTTCCTTTAGCTATGAAATAAATTGTTGCC
GATATCAGATGTTCTGAAATTTATTTGTAGGCCACTATATTTTGAATGATTTCCATGCGCTATGAAGTTAA

FIG. 7B (con't)

TTGACTTGCAACTATGGATTGTTGGTCTATTTGATTCTCTTGTAACCTATTATCAGTTTTTCTTCGATGAA
TGCTTAGGCATGGTCGAATAATGTAACCAAATACCACTTGACCAATTTACTTTCATGGCTACTGAACTAGA
CTAGCGTGCTGATTCGTACATACTGCCTTTGGAAGAACTACAAAAATGTGATCTGACTTTAAGAGTTACTA
AATTAGTACGTAGTAAACTGCAATGCATGGCCAGATCAGCAATTCTGGATTAGCCGGCTGAGTTTTTGAAG
GGCTTAGCAACAAAAATTGACAAGCTTATATATTATAATGGCTTTAAAATACTTGTGTGCATCAGTGAAAA
TCACAATATTTTGATTGCAATAACAAAATGCTATCCTAGATTATTAAGACTTGTTACTAGATTGGTCATTG
ATCTTAAGTTCTTAGGATAAACTGTTGAATCTCCAGTCCTTCGGATTGTATTATGCTACTAATGGCCATTA
AGGATAGCCCCATGACATTAGTTCTCATCTCCAATTTTTCTGTATTGTTTGCGATATTGCTGCAGTTTCTT
ATTACAGCTTGTCTAAGGCTAACCATCTAGGATAAAAAGTAGATCCTGCAGACTTAGAAGATCCAGTTAGG
CTCAATATTCTTATTTTTGTAACTCGGAACTCCAGGACCTCGCTTCAATTTTTTGGCCAATTTTTGCACAA
ACCAAGTTGTAGCTCCAACTGAGGGATCCAACCAGTTCTATCTGATTGCTGACAAACAGATTCAGCATGTA
CGTATGACGAGGACTATTTAAACATGTAATTACTAACCCAAAAAATATTCCAAATTTTATTTAAATATTTA
CCTCCGCTGCAGCATTTTTAATATTACGAAATATGATTTTTACATCTGATAGTAACACTTGTTGCAGTGAC
ATAATTGATTTGAAGTTATGAAAATTCAAGTTCACTGCACAGAACAATCCTTCCTGATTTATGCCCCCGGG
GTAAAGGAGGAGGGTTGTGATAGGCTTGGCGAGCCAACGTAAAAACTCAGCCACTCTTATGGAGATGAAAC
CCAAAAGCCAAAGAGCTAGCTATGGACAGGGGTGCGTGGAAGCTTGCTATCCATGTGCCAGAGCCATGAGT
TGGTTGCGAGATCTTATGGGTTTCACCTCTAGCCTACCCCAACTTGTTTGGGACTAAAGTCTTTGTTGTTG
TTGTTGGTGGTGGTGGTGTCAATGTTGTTAAAGTCTCTTTGTTCATTTCTGAACTAACTTAGCCTATTTGT
AGCATTTCTGTCATTGTTCCTTCCTGTCCCACCCAAAGTTAGTAATGCGATTGTTATTTGTTTGTGCAGGG
AAACTGGTGTCACGAATATAGGAAACTGAAGGCGAAGGTTGAGACAATACAGAAATGTCAAAAGTAATTTG
TAACGATTTTGGTTGATTGCCAGTATATTGTATACACTCTGAAGATAAATGGGACTGAATTTCTACATCCT
GCATCTGCAGGCATCTCATGGGAGAGGATTTTGAATCTTTGAATCTCAAGGAGTTGCAGCAACTGGAGCAG
CAGCTGGAAAGCTCACTGAAACATATCAGATCCAGGAAGGTACTGATTTAAATGATTTGATACAGCAGCAC
AATATATAAAAAAACAAGAAAAACACTTGCAGAGAAGTTCAGCAAAGTATATCTGAAATCAGATTCTAGAC
TGAGATGTTCAAAATATGTATATGCATTTAGTCATATGCTCTTCATAGTTAAAAAAAATGACTAATTTTT
TTCATTTTTTGTACTTGCAGAACCAACTTATGCACGAATCCATTTCTGAGCTTCAGAAGAAGGTAAGCTGT
CAACCTTGCATACCTTATTCGGTATTCGAACTGGTCAACTTGTCATGAAGCCTTAGCTTGTTTCAAGATTT
GTGACATTATAACATGTATGCAAGTAACTGGTCTACATGCACGTAACCTCATTACATCGTTCTTGCTGCAG
GAGAGGTCACTGCAGGAGGAGAATAAAGTTCTCCAGAAGGAAGTAAGCCCGTTATATCACCTTTGGTCCAA
CCGGTCTAAATTGTTCCGTATAGCAAATTTTATTGACAGAGGTCCGTGTCCCTTCCCCACAGCTCGTGGAG
AAGCAGAAGGCCCATGTGGCGCAGCAAGATCAAACTCAGCCTCAAACCAGCTCTTCATCTTCTTCCTTCAT
GCTGAGGGATGCTCCCCCTGCCGCAAATACCAGGTGATGATGTACATCACAAGTCTAATCTTATTCAGAGT
TCAAGTAACCATCTTTTGAATTGGTCGGGTTGTTCCTTGCAGCCCACTTTTGGTCTCTATGCAGTTCTGTC
GGGCCACATTTAAGTAACATAATACTAATATGCTTGTGTTCGCTTTGGTTGTGCAGCATTCATCCAGCGGC
AACAGGCGAGAGGGCAGAGGATGCGGCAGTGCAGCCGCAGGCCCCACCCCGGACGGGGCTTCCACCGTGGA
TGGTGAGCCACATCAACGGGTGAAGGGCATCCAGCCCATACAGGCGTACTATTCAGTAGAGGGT
(SEQ ID NO: 10)

FIG. 8A

CATTCCCACAGGCCACAGCTAGCCATGTCTCGGTCCACGTTAATCATCCTCGCTCTCCTCGCCGTGAGCAG
CGCCGTCGCTGCTCCCCGTGCTCTCGCGGCACGGGAGCTCGCCGGCAACGATGCCATCGCCGTCGACGCTG
CCATGGTGTTGAGGCACGAGAAGTGGATGGCGGAGCACGGGCGCACGTACGCGGACGAGGAGGAGAAGGCG
CGGCGGCTGGAGGTATTCCTCGCCAACGCCAAGTTCATCGACTCGTTTAACGCCCTCACCGTCAGCAGCGG
GGAGCATGGACTGGAGGGCCATGGGCGCCGTCACCGGCGTCAAGGACCAAGGCTCTTGCGGTACGTACAAT
CAACACGACAACACTGGCACGCACGCTACTGCAGATGCATACAAATTAAGCTGCAGAACATTGCAAGCACC
GGAACATTTACCACCTGGATCAAGCTTTTTTAGACTTCTAAAAATGTTAAAAAAGAACTTGCAAGTGGCAA
CACGCGCGTAGGAAAAGTAAAAAATTGACGTGAGATTGTACCGGGATGACTAGAGTCTACAAACAAGTCAT
GCGTGCACTTTTCGGTCAACCCAGACAGCAAGAGGAGTCAGCGTTCACTTTACTTCAATGATTGGAGTATC
ATTCTTAATTTTCCATTTTGGACATGTCCTAAGCTTAATTGCCTCTGTTTCATCATTTAATCAAATAACTT
GGGTGACATGCATATGCAGGCTGCTGCTGGGCGTTCTCGGCGGTGGCGGCGGTGGAAGGGCTGACCAAGAT
CCGCACGGGGCGGCTTATGTCACTGTCGGAGCAGCAGCTGGTGGACTGCGACGTGAACGGCGACGACGAGG
GCTGCGCCGGCGGCCTCATGGACAACGCCTTCGAGTACATGGTCCGCCGCGGCGGCCTCACCACGGAGTCG
TCCTACCCGTACCGCGGCACGGACGGGTCGTGCCGCCGCTCGGCCTCGGCCGCGTCCATCCGTGGGTACGA
GGACGTGCCGGCCAACAACGAGGCGGCGCTGATGGCGGTCGTGGCGCACCAGCCCGTGTCCGTGGCCATCA
ACGGCGGCGACAGTGTGTTCCGGTTCTACGACAGCGGCGTGCTGGGCGGGTCCGGCTGCGGCACGGAGCTC
AACCACGCCATCACGGCGGTCGGGTACGGCACGGCGAGCGACGGCAGCAAGTACTGGATCATGAAGAACTC
GTGGGGCACGTCGTGGGGCGAGCGCGGCTACGTCAGGATCCGCCGCGGGGAGCGCGGCGAGGGCGTCTGCG
GCCTCGCCCAGCTCGCGTCCTCCCTGTCTAG (SEQ ID NO: 11)

FIG. 8B

CATTCCCACAGGCCACAGCTAGCCATGTCTCGGTCCACGTTAATCATCCTCGCTCTCCTCGCCGTGAGCAG
CGCCGTCGCCGCTCCCCGTGCTCTCGCGGCACGGGAGCTCGCCGGCAACGATGCCATCGCCGTCGACGCTG
CCATGGTGTCGAGGCACGAGAAGTGGATGGCGGAGCACGGGCGCACGTACGCCGACGAGGAGGAGAAGGCG
CGGCGGCTGGAGGTATTCCTCGCCAACGCCAAGTTCATCGACTCGTTTAGCGCCCTCACCGTCAGCAGCGG
GGAGCATGGACTGGAGGGCCATGGGCGCCGTCACCGGCGTCAAGGACCAAGGCTCTTGCGGTACGTACAAT
CAACACGACAACACTGGCACGCACGCTACTGCAGATGCATACAAATTAAGCTGCAGAACATTGCAAGCACC
GGAACATTTACCACCTGGATCAAGCTTTTTTAGACTTCTAAAAATGTTAAAAAAGAACTTGCAAGTGGCAA
CACGCGCGTAGGAAAAGTAAAAAATTGACGTGAGATTGTACCGGGATGACCAGAGTCTACAAACAAGTCAT
GCGTGCACTTTTCGGTCAACCCAGACAGCAAGAGGAGTCAGCGTTCACTTTACTTCAATGATTGGAGTATC
ATTCTTAATTTTCCATTTCGGACATGTCCTAAGCTTAATTGCCTCCGTTTCATCATGTACTAATCCAATAA
CTTTGGGTGACATGCATATGCAGGCTGTTGCTGGGCGTTCTCGGCGGTGGCGGCGGTGGAAGGGCTGACCA
AGATCCGCACGGGGCGGTTGGTGTCGCTGTCGGAGCAGCAGCTGGTGGACTGCGACGTGAACGGCGACGAC
GAGGGCTGCGCCGGCGGCCTCATGGACAACGCCTTCGAGTACATGGTCCGCCGCGGCGGCCTCACCACGGA
GTCGTCCTACCCGTACCGCGGCACGGACGGGTCGTGCCGCCGCTCGGCCTCGGCCGCGTCCATCCGGGGGT
ACGAGGACGTGCCGGCCAACAACGAGGCCGCGCTGATGGCGGCCGTGGCGCACCAGCCCGTGTCCGTGGCC
ATCAACGGCGGCGACAGCGTGTTCCGGTTCTACGACAGCGGCGTGCTGGGCGGGTCCGGCTGCGGCACGGA
GCTCAACCACGCCATCACGGCGGTCGGGTACGGCACGGCGAGCGACGGCAGCAAATACTGGATCATGAAGA
ACTCGTGGGGCGCGTCGTGGGGCGAGCGCGGCTACGTCAGGATCCGCCGCGGCGTGCGCGGCGAGGGCGTC
TGCGGCCTCGCCCAGCTCGCGTCCTACCCTGTCTAG (SEQ ID NO: 12)

FIG. 9A

ATCAAGTGGGAAGCGCCATCCAAATTAGCCGAGCTCGCACACTACTGCCGCGTCAGCTCTTGCGGGGAAGA
CGAGCCGCGCCGGAGTGACGTCGTACGGCTTCCCGTTCCCCTCTCGGTTTCCCGACGCCTCTCTTGGCTCA
CCCGCCCGCCCGCCGCCGCCCTGCCACTTCCTCCGCGCGTGAAAGCCCACCGCCTATTCCCCTTCCCTTCG
CTCTCCGACGCCGGGCGCCACCCCGGCGGATCGAGCGGGCGGGCGGTTAGTTAGTTGCGCATCGCTGTTGC
TTGCTTCTTCTACCGTTTGGCGCAGGGAGGAGGAGCGTGGGGGTAACATCGCTGTCCCACTCCCACCCGGG
TGCTGCCCCCTCCTGTTCCCTTCTCACTCACTGCGTGTGCTTATCCGCGCCGGGCGAATCCAATCCCCCAC
TCTCCCCCGTCCTTCTCCAGAAAAGTCGCGGCTTTCCCCCCGCCCCCTCATGATTCCCGTCGATTCCTCCT
CCGCCCATTTGCCCCTCCGCGTCGCAGAATCCCCCGCGCCACCGCTGCTGACCGTCGCGCCGTAGGGGGAG
GGGCAGGAGCGAGGAGCCTAGCTCGGGGGTGGTCGTGGTGGCGACCGGCGGCGAGATGTCGTCGTCGCGGT
CCAACAACCGGCCGGCGTGCTCGCGGGGGAGCTCGGCGCGCTCCAAGCACAGCGAGCGGGTGGTGGCGCAG
ACGCCCGTGGACGCGCGCCTGCACGCCGAGTTCGAGGGCTCGCAGCGCCACTTCGACTATTCCTCCTCGGT
CAGCGCGCTCAACCGCTCCGGGGCCAGCACCAGCTCCGCCGTCTCCGCCTACCTCCAGAACATGCAGCGGG
GCCGCTACATCCAGCCCTTCGGCTGCCTGCTCGCGATCCACCCGGAGTCCTTCGC
(SEQ ID NO: 13)

FIG. 9B

ATCAAGTGGGAAGCGCCATCCAAATTAGCCGAGCTCGCACACTACTGCCGCGTCAGCTCTTGCGGGGAAGA
CGAGCCGCGCCGGAGTGACGTCGTACGGCTTCCCGTTCCCCTCTCGGTTTCCCGACGCCTCTCTTGGCTCA
CCCGCCCGCCCGCCGCCGCCCTGCCACTTCCTCCGCGCGTGAAAGCCCACCGCCTATTCCCCTTCCCTTCG
CTCTCCGACGCCGGGCGCCACCCCGGCGGATCGAGCGGGCGGGCGGTTAGTTAGCTGCGCATCGCTGTTGC
TTGCTTCTTCTACCGTTTGGCGCAGGGAGGAGGAGCGTGGGGGTAACATCGCTGTCCCACTCCCACCCGGG
TGCTGCCCCCTCCTGTTCCCTTCTCACTCACTGCGTGTGCTTATCCGCGCCGGGCGAATCCAATCCCCCAC
TCTCCCCCGTCCTTCTCCAGAAAAGTCGCGGCTTTCCCCCCGCCCCCTCATGATTCCCGTCGATTCCTCCT
CCGCCCATTTGCCCCTCCGCGTCGCAGAATCCCCCGCGCCACCGCTGCTGACCGTCGCGCCGTAGGGGGAG
GGGCAGGAGCGAGGAGCCTAGCTCGGGGGTGGTCGTGGTGGCGACCGGCGGCGAGATGTCGTCGTCGCGGT
CCAACAACCGGCCGGCGTGCTCGCGGGGGAGCTCGGCGCGCTCCAAGCACAGCGAGCGGGTGGTGGCGCAG
ACGCCCGTGGACGCGCGCCTGCACGCCGAGTTCGAGGGCTCGCAGCGCCACTTCGACTATTCCTCCTCGGT
CAGCGCGCTCAACCGCTCCGGGGCCAGCACCAGCTCCGCCGTCTCCGCCTACCTCCAGAACATGCAGCGGG
GCCGCTACATCCAGCCCTTCGGCTGCCTGCTCGCGATCCACCCGGAGTCCTTCGC
(SEQ ID NO: 14)

FIG. 10A

CTGATCTGCTTGCAGCAACCCGGGTACGACATCATAGCGCAGTTCATGATCGGCTACGCGCTACCCGGCAA
GCCCATCGCCAACCTGCTCTTCAAGATCTACGGCCGGATCAGCACCGTGCACGCGCTCTCCTTCCTCGCCG
ACCTCAAGCTCGGCCACTACATGAAGATCCCGCCACGCTGCATGTACACCGCCCAGGTACGTGACAGAGAT
CGATCTCTCAGCCCCCACAATGCACTAGATGCTCATCACTCGCTGAACTAACCGGCGTGCGCTTGGCCGGT
GCAGCTGGTGGGCACGGTGGTCGCCGGCGTGGTGAACCTGGCGGTGGCGTGGTGGATGCTGGACAGCATCG
ACAACATCTGCGACGTGGAGGCGCTGCACCCGGACAGCCCCTGGACGTGCCCCAAGTACCGGGTCACCTTC
GACGCGTCGGTGATCTGGGGCCTCATCGGGCCGGGGCGCCTCTTCGGCCAGCACGGGTTGTACCGGAACCT
GGTGTGGCTGTTCGTGGTCGGCGCCGTGCTGCCGGTGCCGGTGTGGCTGCTGAGCCGGGCGTTCCCGGAGA
AGAAGTGGATCGCGCTCGTCAACGTGCCCGTCATCTCCTACGGCTTCGCCGGGATGCCGCCGGCCACGCCC
ACCAACATCGCCAGCTGGCTCGTCACCGGCACCGTCTTCAACTTCTTCGTCTTCAGGTACCGCAAGGGGTG
GTGGCAGAAGTACAACTACGTGCTATCGGCGGCGCTCGACGCCGGCACCGCCTTCATGGGGGTGCTCATCT
TCTTCGCGCTCCAGAACGCGCACCACGACCTCAAGTGGTGGGGCACCGAGGTCGACCACTGCCCGCTCGCC
ACCTGCCCCACCGCGCCCGGCATCGTCGTCAAGGGCTGCCCGGTCTTCTGAGCACTGAGCTCGCCGGAGCA
TCATCGGACACTGCCCGCCATGTATG (SEQ ID NO: 15)

FIG. 10B

CTGATCTGCTTGCAGCAACCCGGGTACGACATCATAGCGCAGTTCATGATCGGCTACGCGCTACCCGGCAA
GCCCATCGCCAACATGCTCTTCAAGATCTACGGCCGGATCAGCACCGTGCACGCGCTCTCCTTCCTCGCCG
ACCTCAAGCTCGGCCACTACATGAAGATCCCGCCACGCTGCATGTACACCGCCCAGGTACGTGACAGAGAT
CGATCTCTCAGCCCCCACAATGCACTAGATGCTCATCACTCGCTGAACTAACCGGCGTGCGCTTGGCCGGT
GCAGCTGGTGGGCACGGTGGTCGCCGGCGTGGTGAACCTGGCGGTGGCGTGGTGGATGCTGGACAGCATCG
ACAACATCTGCGACGTGGAGGCGCTGCACCCGGACAGCCCCTGGACGTGCCCCAAGTACCGGGTCACCTTC
GACGCGTCGGTGATCTGGGGCCTCATCGGGCCGGGGCGCCTCTTCGGCCAGCACGGGTTGTACCGGAACCT
GGTGTGGCTGTTCGTGGTCGGCGCCGTGCTGCCGGTGCCGGTGTGGCTGCTGAGCCGGGCGTTCCCGGAGA
AGAAGTGGATCGCGCTCGTCAACGTGCCCGTCATCTCCTACGGCTTCGCCGGGATGCCGCCGGCCACGCCC
ACCAACATCGCCAGCTGGCTCGTCACCGGCACCGTCTTCAACTTCTTCGTCTTCAGGTACCGCAAGGGGTG
GTGGCAGAAGTACAACTACGTGCTATCGGCGGCGCTCGACGCCGGCACCGCCTTCATGGGGGTGCTCATCT
TCTTCGCGCTCCAGAACGCGCACCACGACCTCAAGTGGTGGGGCACCGAGGTCGACCACTGCCCGCTCGCC
ACCTGCCCGACCGCGCCCGGCATCGTCGTCAAGGGCTGCCCGGTCTTCTGAGCACTGAGCTCGCCGGAGCA
TCATCGGACACTGCCCGCCATGTAG (SEQ ID NO: 16)

FIG. 11A

GTTCTCACATTTCGTGGTTGTTTGTCCTGGGACTTTCATTCTGCAGTTGGTTTTCTCTGGACATGCCTCTG
GGAGGCTCTTGAAATACAATCCCGAAACAAAGGAGACAACAGTCCTTCACCGCAACCTCCAGTTTCCCAAC
GGAGTGAGCTTAAGCAAGGATGGCTCGTTCTTCGTCTTCTGTGAAGGATCTCGTGGAAGGTCTATACACTC
TTCCCTCCATTTGGTTCAGGATTTCATACATGTATACTTGAAATTAGTCACTGATTATTGTGTCCTTATCC
AAACAGGTTGAGCAGATACTGGCTGAAAGGTGAGAAGGCAGGCACCGTCGATCTCTTCGCCATCCTGCCTG
GGTTCCCGGACAACGTGAGGACCAACGACAAGGGCGAATTCTGGGTGGCCATCCATTGCCGACGCAGCGCA
TACGCCCGGCTCTTGAGTCGCCGCGTCCAGCTCAGAAAGTTCTTGCTCAGCCTCCCGATCCCCGCCAAGTA
TCACTACCTGATGCAAATCGGCGGCAATCTGCACGCGCTCATCATCAAGTACAGCCCTGAAGGCGAGGTGC
TTGACATCTTGGAGGACACTAAAGGGCAGGTGGTGAGAGCTGTGAGCGAAGTGGAGGAGAAGGATGGCAAG
CTCTGGATAGGATCTGTTCTCATGCCCTTCATTGCCGTCTTTGACTACGCCAAGGAATCCTAAGCCGCCCT
TTTGCCGGGATACATGGGTAAGAGAGTATGAAATCCACGAACGCCGTTGCACACTATTGCTTCATCCAAAT
AAATCTAGTGTTGGAAGCAACCTAGAATTGCTTGATGTTTCAGCCTTTTCCTAGTAGCAACTGTAACTCAC
TGACATTTTAGTTTGTCCCTGGGATCTTTCAA (SEQ ID NO: 17)

FIG. 11B

CGGCAGCACTTTTCATGATGTTTGTCCTGGGACTTTCATTATGCAGTGGGTTTTCTCTGGAGATGCCTCTG
GGAGGCTCTTGAAATACAATCCCGAAACAAAGGAGACAACAGTCCTTCACCGCAACCTCCAGTTTCCCAAC
GGAGTGAGCTTAAGCAAGGATGGCTCGTTCTTCGTCTTCTGTGAAGGATCTCGTGGAAGGTCTATACACTC
TTCCCTCCATTTGGTTCAGAATTTCATACATGTATACTTGAAATTAGTCACTGATTATTGTGTCCTTATCC
AAACAGGTTGAGCAGATACTGGCTGAAAGGTGAGAAGGCAGGCACCGTCGATCTCTTCGCCATCCTGCCTG
GGTTCCCGGACAACGTGAGGACCAACGACAAGGGCGAATTCTGGGTGGCAATCCATTGCCGACGCAGCGCA
TACGCCCGGCTCTTGAGTCGCCGCGTCCAGCTCAGAAAGTTCTTGCTCAGCCTCCCGATCCCCGCCAAGTA
TCACTACCTGATGCAAATCGGCGGCAATCTGCACGCGCTCATCATCAAGTACAGCCCTGAAGGCGAGGTGC
TTGACATCTTGGAGGACACTAAAGGGCAGGTGGTGAGAGCTGTGAGCGAAGTGGAGGAGAAGGATGGCAAG
CTCTGGATAGGATCTGTTCTCATGCCCTTCATTGCCGTCTTTGACTACGCCAAGGAATCCTAAGCCGCCCT
TTTGCCGGGATACATGGGTAAGAGAGTATGAAATCCACGAACGCCGTTGCACACTATTGCTTCATCCAAAA
TAAATCTAGTGTTGGAAGCAACCTAGAATTGCTTGATGTTTCAGCCTTTTCCTAGTAGCAACTGTAACTCA
CTGACATTTTAGTTTGTCCCTGGGGATCTTTCAA (SEQ ID NO: 18)

FIG. 12A

CGCGCCAGGCCGCCGCCCACACTTCCCGCCGAGCCTAAAAGATGCAAGAAGAGAGAGGGGAGAGGCTAGAG
GGTGATGGAGGGGCTCACCGCACCAATAACAATGGATAGCGCTGCTGCGGTGGATTTCCCTCTGGCTGAAT
TTGTCCCCCACCCCACCCGCTCACCCACACTCGCGTGAATTGATTTGCGCCATTCGCCGTTGCCGTCTGTT
TTTAATCTTTTTCAAGCGGGTGCAGGTGAGCTCGGGCCCGACTGAGGGCCTTTTTGATTCATAGGATTGCA
AAAACACAGGAATAGGAAAAACGCAGGATTGAAATGGCATGTCCATTGGATCCCTATAGGATTTGAGTTTG
TTTGATTGTGTTAAGGGAAAAACAAAGGATTTTTTTTCAAGAGGTTTGAGTGGATGCTAGAATTTCTGTGA
AATGTAGTACAAATGAACCCTTAGAAAAAAATACAGGATTCAATCCTACGAATCAAACGATCAACGTAGAA
AAAATTCCTAAGGATTCTAATCCTTCAAAGATCTTATGAAAATCCTTTGAATCAAAGAGACCTTGAAGTTG
TGGAGCTCAAAATTTATAGTATTCCTCTAGAAGAAGCTCGAAATTACTTCTATACTGATTAACTGATGTGT
GTGCAAAAAGAAAAGAACTGATTAACCGATGAAACAACCAGTGTTTGGTACACTTCTGCGGGGGTGAATTG
GTGAGCTGGACAGGGCCCACCCGCAGCAAATTGCTTCTATTATGGTGGCCGCCTCCTCTCCTCTCCCTGGC
CAGATCCCAAATTTGAAATCGCCCAACGTCTCCAGACTCCTCTCCGCTCCCCATTTCAAAACCTCCAATCT
CGTCCTCTCCCCACCCCCACCCACCGCCGCCGGCCCGCCGCGCCGCTGCTCTGCCCAGATCCCGCCCGCCG
CAAGCCCATCCCTGCCTCCGTCGCAGCCGCAGCGGTACCCGCAGCCGCAGCCGCGATGCTGTCGGACGGTG
GCGACGACGACAGCTCCGCCCCCGCGCGGTTCGAGCTGCAGGAGGACCCCTCCTTCTGGAAGGACAACAAC
GTGCAGGTAGTGATTCTTCTCGCCCCCCTCGCCGGGAGCTCCCGCGCCTCCGCCTCCTCGATTCTCCCCTG
GCAGCGGCGTCCCGATCTAGTTTCGCCCGCGGCCGCGCGCTGCGCCGTTGGATCATTTCGTCGAGCACCTA
GGTTCGTCAGGTCCGGTCCGCGCTAACCGCTCCGCCCCGCAGGTCGTGATTCGTGTCCGGCCGCTCAGCAG
CAGCGAGATATCGGTGCAGGGGGACAAGAGGTGCGTCAGGCAGGACAGCGGCCAGAGCATTACCTGGACCT
GCCACCCGGAGTCCCGGTTCACCTTTGATCTAGTCGCCGATGAGCACATCACGCAGGTATACTCCTTGTTC
CTGTTCGCCCGTTCCTTTACTTGTTCCGCAGATGTGTAAATACTCTTGTGCTTGTGCTGTATAGGAGAGTC
TTTTCAAGGTTGCTGGGGTGCCCATGGTGGAGAACTGCATGGCTGGCTATAACAGCTGCATGTTTGCCTAT
GGGCAGGTGAGCTACAGCCTCCACCTCCACCTGCTGTTGCAGTGTGCTTACTCTCTTTTATTTGCACTTTG
AATCATTGAGCTTACAAAAGTATCCTGTTTCTTAGACCGGTAGTGGCAAGACCCACACGATGCTTGGGGAC
ATAGAAAATGGCACACGGGGAAACAATGAGAACTGTGGTATGACGCCTCGAGTGTTTGAGCATCTCTTCCT
AAGAATCCAGAAGGCAAGCTCTGATGATATGTTGATTCTGATGCCTAATTTTGTGCTGTAGATGGTGTACT
GTTTCTGAGGTAAACTTTTCAATTGCTGTTTGCAGGAAAAGGAAATACGAAGAGATGAAAAGCTCAGTTTT
ACTTGCAAGTGCTCATTCCTGGAGATATATAATGAGCAGATTCTGGATTTGCTCAATCCAAATGCAACAAA
CTTACAGGTAATTCACTGAAATCTAGTGTCTGCGTATACCTATTTGGTGGTTGCATCTTTGTCGTGACACT
GTTGGGAAAAGTTTACAAAGTTTGCATCTAACTTACAGCTATGCTTTTCTTTTACAGTTAAGGGAGGATGC
GAAAAGGGGTATGCATGTTGAGAATCTGACTGAACATGAGGTTTCTAATGCCCGAGAAGCACTGCAACAAC
TTATCGAGGTCAGTGTCCCAAAAACAGCGTAGTAGGCCTGATTTTGGCAGTACCTGTGTCGATGATTGCAG
AATGATTAATATAACATGCCTACATCAATTTTGCTCAaGGTTCTTCGCACAAACAGTCAAATACACACATA
TAAACTAAGTGTATAAATATAAACATGCTTTTTTCAATCTCCAATTCCTTGTCTCCTTGACTTCTCTTTTG
ATCGTTTTAGCAACTGTCACTGACAATTACAGCCACTTACTTTTCAAAACTATATACTTAAACATTACACA
ATACAGTTTTCTTTTGATGCAGTATGAATAGAAATCCGTAAATATGAATTTTAAATAGGAAAAACAATTAG
CATATTATACTTTACTGACAAGATGGAGTGACTGAACTATTTAGAACATGGACTGCAGTTAAGCTGATCAG
ATCCATCATTTTCGCATGGCATGTTACACTAGTTTTTCCTTTATCTCTAGGGATTGCAGCAAGTTTTTCCC
TCCCTTTATTAGTCACATTATTATCTGTGTTAGTTTCACTAAATCACTAGCTAAATTCTGCATTTTCTCTT
CAGGGGGCAGCAAACAGAAAGGTGGCATCTACCAATATGAACCGAGCAAGTAGCCGTTCTCATAGTGTATT
CACTTGTCTTATAGAGAGCAAGGTATAGTTTTTGTGTAATAGGAAGCAAAACATTCTTGCCTTAACTTTCA
AAGATATTGCTAGACCAGCATATATTTGTCCCTACCTTAATGCATGCATATGTATTGATGCACTTAATCTT
CTAACTGAACTATCAACCTTACAGTGGGAATCTCAAGGTATCAAGCATCATCGATTTTCTCATCTTAACCT
TGTTGACCTTGCTGGCTCAGAGAGGTAAGTTCCACATGTAACCTTGCTTTTTTTTGTTACGTATGATCTTG
TATTTCAGAGCCACCACAAATATACCTGTTATGCTTCTCAAGTCTCCTATTCTTGCAACTGAACGTGGATG
ATGTGTGATGTGCAGGCAAAAGAGTTCAGGTGCAGAAGGGGAACGCTTGAAGGAAGCTTCGAACATCAACA

FIG. 12A (con't)

AGTCACTCTCAACCTTAGGGTTAGTTGTGGAGCTTCAATTCTTTACCTCAGATAATACTAAACTGTTCATA
GCTTGACTTGATTCAGTTTAATCATTTCACTGTTTCCCTATGGGATTGTTACAGACATGTTATTACCAGCC
TTATTGCTGTGTCAAACAAAAAGTCACAGCATGTTCCCTACCGAGATTCAAAATTGACATTTCTGCTGCAG
GTAATATGCACAGCTGAAGTGGTAGATTTCTCACGTTATGTTTTGACATCTCTGATGTTAACTTTGTTTA
TTTATACATTTTCATCTCTTTCCAGGACTCACTTGGAGGTAACTCCAAGACCACTATAATTGCAAATATAA
GCCCATCTAGCTGGTAGACTTCTAAACACGATTTCTTTTTCCTTTTCTGCAAAAGGCTTGCTATAGTTACA
TGCATCTTACTGATATTTTAATTGTATTTCTAGCTGTGCAGCTGAGACATTGAGCACATTAAAATTCGCG
CAACGGGCTAAGCACATACGGAATAATGTATGTCATGAACATGTCTTATTGACTTGTTTTAATATGCAAA
ACAATAACTAATTGTTGTTTTTGTAGGCTATTATAAATGAGGATGCCTCTGGTGATGTGCTGAGCATGCGT
TTAGAGATCCAACATCTCAAGGTATAGATGATGAATTTCAATTTCGGTTTAATGAAAAATATTCTGTGCAC
TGGATTGCAATAAGTTCCAGGTTAACATGTTTCTTCTAATTATGGTCCTTTGTGCTATGATTGACGTTTGT
TGTTAATTAACAGTGGCCTGTGCCTGATATTTTTTGTTGCAGAGCGTTAATATGTTTTGTTGTACACAATC
TAATGCTTTGCTATTACCACAGAAAGAGCTTAGTCGCCTGCAAGGACAATCTGGATTTACTAACAATGGAT
TTGTCTGCGAGTCCCCTAGCGCATTCAAATGGGATCAAGCTAATGGCACATTCAGTCCACTTATGTTTGAT
AAGAGAGCTACACAGGTATTCATATACTGTTTTGTCTATATCGAACATTATCCATGTACTGGTTCTGTTTG
TTGAACTTATGTTTTTAACCGTATGCTTACTTTCTCTTTCTCGTGTTGTGTTCAGAGGAGAGATTATGATA
TTACACTTGCCGCTGCATTTAGGAGGGAGCAGGAAAAAGAAGCAAAGCTAAAGGCAGCAATTGCTGCAAAG
CAGATTGCCGAAGAGCTGGTATGCATCTCTCTTCACTACATTAGATTTTGTAGATACTCTAGAACACTTTG
TCACTAAAAAAAGCAAATATATGCCAGTATAGTATTTTTTTTTCTTAATGTCAATTTGTTGTTGCACCACAG
GTGACTCAAAGATCAGAAGAGGTGAGAAGTTTCAGGATGAGGCTTCGCTTTCGTGAAGATCGAATCAAGAG
ATTGGAGCAAGTTGCATCGGGGAAGTTATCCGCTGAAGCACATCTCTTGCAAGAAAAGGAAGACCTCATGA
AGGAAATTGAAGCTCTACGGAACCAACTAGAACGAAATCCAGAAATTACAAGATTTGCTATGGAAAATCTA
CAACTGAAGGAGGAGATTCGAAGGTTAGCTTCGGTATCCAATCACTTCAGTTGCCCCCCTTTTCTACTGCC
TACACTAATATAGTTGGTAGCTTGATGCCTTTTTTTTTGAACTTGTAGGTTGCAGTCATTTGTTGATGAAG
GAGAATTGGAAAGAATGCATCAGCAGATAAATGTTTTAGAACATCAGGTATCCACTTTTGTGAAGGGGAAT
TTTTCAGTGATAAATTTTTTTTGTACTAAAATGAACTTTTTTTACTCTTATAATTTCTTAACATCCTGA
ACTTACTTAGTTTGTTTTCCTTTAGCTCCTAGAAGCACTTGACTGGAAACTTATGAATGAGAAGGATCCTG
TTAACAAGGTATGCTATATAATTTGTAGACTTCAATCCTGTTTAGTGAAAATATATGCAAAACTTTTGAAT
TTTCTTTAGCTAGCTGTTACAAATACTTGCATGGCATTATATCTCTTTACCTACCATTTTGCTTAGACGAT
ATCCCATAATGACTTCTACAGGACCTCTCACTATTTGGGGAGGAAGCTGGTGATGAGAAAAACGAGTTTCT
TCTTGTGCAGGTTGGTATTGTAGAACTATATTTGGCATATCGTCTGATGATATCTTCACAGATCTTTTAAA
ACAACCTGTAAATTAATCATAAGTGTACATTGTTGATCAACTCCGATACGGAGGAGGTAGCTGACTTAATA
AGTATCCTATTCTGATTCATTTTTTTCTGTAACATCAGTTTGTAATGTTGTTATACAGGCTATCCAAAATG
AGAGAGAAATCGAGTCACTACGTAAAAATTTGAGCGTCTGTCTTCAAGCAAAAGAGAAACTCGAGAGGTAT
ATCACTATTTCTTGTCTGTGTATTCTGTTATTGCATGCTATGGTTGTGTGGTATGATGAGAAAGGAATATC
ACTATTTCTTGTCTGTGTATTCTGTTATTGCATGCTATGGTTGTGTGGTATGATGAGAAAGGAATATTAAT
GTCATCAGCTTTTGCAATCATAATTAGTTCCTTAAATTTACAGTATTTACTTCAGGCCCCATGGTAACACA
ACTCTCACATATGTAAAACCCTTGGTGCCCCACAAACAAGATTAGAGGTGTATAGTATCTAGAAGTAAAAA
AACACTTTGTTGTTAGTGTTTCAAGTCACTGTAACTGCAGAAATTGTTGTGCTGTTTTTGCGCGCTACATT
TCAAGACCTACCATTTGGTTCTTGGTGTTCTTCTTGTTGTTGTTTTTTATTCTCCTTAGGAACGAAGCCTA
TAATAGTTGGTGGGAGGTCACCCAGGTTTGAGTTCCCCTCAACCTGAATCTGGGTGCTTATCTCTCCATCA
CTGAAAAGTTTCTTAGTTCCTTCCAGGCAATCTAGTATTTTTTTCTGCTTGGTAGTACTGTGCATATCGAA
TGGATAATATGCTTAGAATAGTTGGTGGGAGGTCACCCAGGTTTTGAGATATCAATTATTTAGTGGTTGGA
GTTAATGATGCATTTGTGCAAGTTCAAGAAAAGGTGTGCTTCTCAGAAGGGGTGATGGCTAGCGTAGGTGT
AGATCAACCACAACAACTCATCTGTGCTGCATTTGTTTGATTTACTTGCATATGATATCCCAAGAATTAT
AAAAAGGCCCTAAAGAGTATGGCAAGTCATTTCTAAATCATCTTGGTTTGCAAGCTTCACTGATGGTTTTC
ACTGCATACTATTTTGTGTGTCCGGAATTATGTTCCTTTTTTTTGCTTTGTCTTGTCCAGAGATTTATGTG
GTTCATTTCTCACATTGGATGTTGTGCAGGCGTGTTGATGATTTGACTGTGGAGTTGGAGGTAGCGAAGAA
ATGCGACCATGAGAACAAAGAATTTAAGGCTGCACAGCACCAGGAACAGTCCGTCTTGCTTGATGCTCAGA
CAGAACTTAAGACATTGGTAGATGCAATAGCAACTGCAAGTCAAAGAGAAGCAGAAGCTCATGAAACTGCA
ATTGGGTTGGCCAAAGAGAATGAGAAATTGAGAACAGAGCTTACGACCCTGATCGAGGATAACAAGAGACT

FIG. 12A (con't)

GGTTGATCTCTATGAACAGGCTATTGTCAACATTGAGGTGAAACAACATGGAAATTATCCTTCCATTCCTC
AAACTGAAGATTCGAATGAGCAGCAGAGCAGCCATCCTTCTAATGGAGGGAATAGCCTGCTGGATGACCAA
CCAGAGGGTGCATATGGTTCACGTAGTGATGCTGTAGAAGAGCCTATGATAGTGGATGAAAACTGCAGCCA
CAAGGATGACCCTTCGAGATCTGAATtTTCAGAACTGCAGCTTCAACTGGAAGAGATGCATGAAGAAAATG
ATAAACTTATGAGTTTGTATGAGAAAGCAATGCAAGAAAGGGATGAATTTAAAAGGAAATTTTCTGAGCAA
AGCAATCATGAAACCACAGAAGACGTTCAGTTCAGAGATGCTGAAATGGATGAAGCAATGGATACCATGCA
AAGCAATCCTGAAACTACAGAAGACATTCAGTTCAGAGATGCTGAAATGGATAGTATGCTAAGCAATCTTG
AAAGTTCAGAAGACATTCAGTTCAGAGATGCTGAAACCGATGCTGAGGGTTTCCAAGGAGAGCATGTACAT
GACTCTCCAATTGTAGCTTTCAAAGAAGCGATGCAGCTTGTCCGTGTCAAGCTGGAGCATGTCCAAGACAA
GCTTGTGACTGCCCAGGATGCAGTGCAATATTTCAAGCTACTTGAAATGGCTAGCACCAAGGCAGAAGAAC
TTTCATCAAGCATTCAGCTCTGCTGTCTAGATGTCCAGAAAGAGCAGGAAGACATCAACGCCCTCAAGTCC
GCACTGTCAATATCACACGAGAGAGAAAACGCTTTGGAAGGCAAGTTTTTCTCGCCTGTGGCATCATGCCG
GGACTTGCATTTGAAAACCGAAGCCCTTGCCGGGTCCAAGTTTGGCGTCAATGTTCAATCAATGAATAAAA
AGATGGAGCAGTTGAGTAGGTTGAGAACTCGCAAAACCGAGATTTCCGCTGCACGTGCAGAGGCACGCAGG
TCTGAAACCGAGCTGAGAAACAAAATCGATGGCCTTAAACAGAAATACCGTTCCTTCGAGGCCCAAAGGAA
GGAGACAGAAAGGGTTCTCTTCGCCATCGACAACCTGGAGTGCCCCGCGACTCCGTTGCAGAAGCCCATGA
ATTTCGGCAAGGCGTCGGAGCTGCTGAAGTCCGAGGAGGAGAGGACAAAGCTCTTGTCTGAACTGAAGAAG
TTCCGCGAGCAGCTTAGCGTGGTGCAGAAGGAGATCAAGAGCATGAGGAACTGCGACGACATCGACGGTGA
GATGTCGCGCCTTGAATCGGAGATGGAGGGCTGCTTCCTCTCCCTGCTGGAAGCCGAGACCGAGAAGTTTG
TGCGGGATCACACCTTGGCCGAAGTCTGGGAGGTTCAGCAGAAGGACTTGCCGAGCCTACTGGTCGACTAC
CAGGACAGCGTTTTCCATGTGAAGCTGGAGGAGGAGCAGATCAGGGTGTGCGAGGCGTCGTTGCAGCACCA
GACGACGTCCCTGGACGAGATGAACTCGAAGCTGAGCCAGGCGATGCGGGACCTCGGCGAGCTTCTGGTTG
CCAGAGGTTTGGACGCCTCCACGCCGCACGTCTCCGACAAGGTGAAGGGGGACCTCGACGCCATCGAGGCC
CATGTCGCCGAGGCCAGGCAGCTCTTGCTCGTCGACAACCAATAAGATTTGCTGCGAACCAAAGCAAACCG
GTTCTCGCCATTGACAGACAGGCTGGTCTGTCTCCGCCTTCATTTTGTACAAATTCTTTGTAACGGAACGT
TGGTTCTCTCGGGTGCTGTTATCTGTGATTCGATTCTGTAGTTTGGATGGATGGGTGGATGTAGGTCCTGA
AGTGGACTGTAATAACTGTTCTGCGCGGCCTCTTGTTCTGTTCTCTGGTGGTCTGGCATCGAAGCTTCTTC
CAGAAGGCCGTTGCTAAGCTATGCAACTATAGATTCACCTCCTTCTGGTATGCACTTGGCCGTGCAAGACA
GCAATGATTGGACAATGTCGATTTCAAGAGGGCTTGACTATTTTGTTGTTTATCATAATCTGTGGCAGCGA
GCGTGGTTGCGTGTGTTCGTGAAGAAAAGAATGCCGGTGTTTCAGTTCATCGCAGGAGGTTGCAGGCCGAG
AAACTTGTTTTCCATTATTGTACTACTACATTTGGTGTTAACTTGGGCTGTGTCGTGGCGGTTGAGAAATG
TGTTCTGCAGGTCCTTGAGGGCATTAGGGCAGGTACAACGGTGTCCAGTCAGCTGTCTGGAAGGGGTGACA
GCTAGGATTTTAGATGATGTGGAGGAGAGAGAACAAAGAAAGAGAAACAACCCGTCTGTAGAATAACCAAC
GATCTGCAGCCCTTAAAATCCGGTGGATACAGATGGCCTTCTACCGTTGTATGGGGTGCCGTCTGCAAAGT
TGTTTGTAACTGCCTCCTTTGTCCCTGGATTAGTCTTCCACTCATCAATATTTGACAGTAAAATAGACGGT
CTAATGTATAGGGTGTCTTAATCTCTGTATATATACGTGATGTGGAGCATCGTTACAGACAACGAGTTGTCTG
AACTAATGTAAATGCCCTCATGCTCCATGCTGCCGCCAGGTTCGGTTGTTTGGATTGCTTCTGGAAGCTCC
TTGAGCTATTTTTGTCTCTTCAGGGTTGCTTCTTTGCCTCTTTGTGTCCACTTGTTTGGTTGGACTGCTCG
GCTCGCCTATTTGGTCGTTGTTTTTC (SEQ ID NO: 19)

FIG. 12B

CGCGCCAGGCCGCCGCCCACACTTCCCGCCGAGCCTAAAAGATGCAAGAAGAGAGAGGGGAGAGGCTAGAG
GGTGATGGAGGGGCTCACCGCACCAATAACAATGGATAGCGCTGCTGCGGTGGATTTCCCTCTGGCTGAAT
TTGTCCCCCACCCCACCCGCTCACCCACACTCGCGTGAATTGATTTGCGCCATTCGCCGTTGCCGTCTGTT
TTTAATCTTTTTCAAGCGGGTGCAGGTGAGCTCGGGCCCGACTGAGGGCCTTTTTGATTCATAGGATTGCA
AAAACACAGGAATAGGAAAAACGCAGGATTGAAATGGCATGTCCATTGGATCCCTATAGGATTTGAGTTTG
TTTGATTGTGTTAAGGGAAAAACAAAGGATTTTTTTCAAGAGGTTTGAGTGGATGCTAGAATTTCTGTGA
AATGTAGTACAAATGAACCCTTAGAAAAAAATACAGGATTCAATCCTACGAATCAAACGATCAACGTAGAA
AAAATTCCTAAGGATTCTAATCCTTCAAAGATCTTATGAAAATCCTTTGAATCAAAGAGACCTTGAAGTTG
TGGAGCTCAAAATTTATAGTATTCCTCTAGAAGAAGCTCGAAATTACTTCTATACTGATTAACTGATGTGT

FIG. 12B (con't)

GTGCAAAAAGAAAAGAACTGATTAACCGATGAAACAACCAGTGTTTGGTACACTTCTGCGGGGGTGAATTG
GTGAGCTGGACAGGGCCCACCCGCAGCAAATTGCTTCTATTATGGTGGCCGCCTCCTCTCCTCTCCCTGGC
CAGATCCCAAATTTGAAATCGCCCAACGTCTCCAGACTCCTCTCCGCTCCCCATTTCAAAACCTCCAATCT
CGTCCTCTCCCCACCCCCACCCACCGCCGCCGGCCCGCCGCGCCGCTGCTCTGCCCAGATCCCGCCCGCCG
CAAGCCCATCCCTGCCTCCGTCGCAGCCGCAGCGGTACCCGCAGCCGCAGCCGCGATGCTGTCGGACGGTG
GCGACGACGACAGCTCCGCCCCCGCGCGGTTCGAGCTGCAGGAGGACCCCTCCTTCTGGAAGGACAACAAC
GTGCAGGTAGTGATTCTTCTCGCCCCCCTCGCCGGGAGCTCCCGCGCCTCCGCCTCCTCGATTCTCCCCTG
GCAGCGGCGTCCCGATCTAGTTTCGCCCGCGGCCGCGCGCTGCGCCGTTGGATCATTTCGTCGAGCACCTA
GGTTCGTCAGGTCCGGTCCGCGCTAACCGCTCCGCCCCGCAGGTCGTGATTCGTGTCCGGCCGCTCAGCAG
CAGCGAGATATCGGTGCAGGGGGACAAGAGGTGCGTCAGGCAGGACAGCGGCCAGAGCATTACCTGGACCT
GCCACCCGGAGTCCCGGTTCACCTTTGATCTAGTCGCCGATGAGCACATCACGCAGGTATACTCCTTGTTC
CTGTTCGCCCGTTCCTTTACTTGTTCCGCAGATGTGTAAATACTCTTGTGCTTGTGCTGTATAGGAGAGTC
TTTTCAAGGTTGCTGGGGTGCCCATGGTGGAGAACTGCATGGCTGGCTATAACAGCTGCATGTTTGCCTAT
GGGCAGGTGAGCTACAGCCTCCACCTCCACCTGCTGTTGCAGTGTGCTTACTCTCTTTTATTTGCACTTTG
AATCATTGAGCTTACAAAAGTATCCTGTTTCTTAGACCGGTAGTGGCAAGACCCACACGATGCTTGGGGAC
ATAGAAAATGGCACACGGGGAAACAATGAGAACTGTGGTATGACGCCTCGAGTGTTTGAGCATCTCTTCCT
AAGAATCCAGAAGGCAAGCTCTGATGATATGTTGATTCTGATGCCTAATTTTGTGCTGTAGATGGTGTACT
GTTTCTGAGGTAAACTTTTCAATTGCTGTTTGCAGGAAAAGGAAATACGAAGAGATGAAAAGCTCAGTTTT
ACTTGCAAGTGCTCATTCCTGGAGATATATAATGAGCAGATTCTGGATTTGCTCAATCCAAATGCAACAAA
CTTACAGGTAATTCACTGAAATCTAGTGTCTGCGTATACCTATTTGGTGGTTGCATCTTTGTCGTGACACT
GTTGGGAAAAGTTTACAAAGTTTGCATCTAACTTACAGCTATGCTTTTCTTTTACAGTTAAGGGAGGATGC
GAAAAGGGGTATGCATGTTGAGAATCTGACTGAACATGAGGTTTCTAATGCCCGAGAAGCACTGCAACAAC
TTATCGAGGTCAGTGTCCCAAAAACAGCGTAGTAGGCCTGATTTTGGCAGTACCTGTGTCGATGATTGCAG
AATGATTAATATAACATGCCTACATCAATTTTGCTCAaGGTTCTTCGCACAAACAGTCAAATACACACATA
TAAACTAAGTGTATAAATATAAACATGCTTTTTTCAATCTCCAATTCCTTGTCTCCTTGACTTCTCTTTTG
ATCGTTTTAGCAACTGTCACTGACAATTACAGCCACTTACTTTTCAAAACTATATACTTAAACATTACACA
ATACAGTTTTCTTTTGATGCAGTATGAATAGAAATCCGTAAATATGAATTTTAAATAGGAAAAACAATTAG
CATATTATACTTTACTGACAAGATGGAGTGACTGAACTATTTAGAACATGGACTGCAGTTAAGCTGATCAG
ATCCATCATTTTCGCATGGCATGTTACACTAGTTTTTCCTTTATCTCTAGGGATTGCAGCAAGTTTTTCCC
TCCCTTTATTAGTCACATTATTATCTGTGTTAGTTTCACTAAATCACTAGCTAAATTCTGCATTTTCTCTT
CAGGGGGCAGCAAACAGAAAGGTGGCATCTACCAATATGAACCGAGCAAGTAGCCGTTCTCATAGTGTATT
CACTTGTCTTATAGAGAGCAAGGTATAGTTTTGTGTAATAGGAAGCAAAACATTCTTGCCTTAACTTTCA
AAGATATTGCTAGACCAGCATATATTTGTCCCTACCTTAATGCATGCATATGTATTGATGCACTTAATCTT
CTAACTGAACTATCAACCTTACAGTGGGAATCTCAAGGTATCAAGCATCATCGATTTTCTCATCTTAACCT
TGTTGACCTTGCTGGCTCAGAGAGGTAAGTTCCACATGTAACCTTGCTTTTTTTTGTTACGTATGATCTTG
TATTTCAGAGCCACCACAAATATACCTGTTATGCTTCTCAAGTCTCCTATTCTTGCAACTGAACGTGGATG
ATGTGTGATGTGCAGGCAAAAGAGTTCAGGTGCAGAAGGGGAACGCTTGAAGGAAGCTTCGAACATCAACA
AGTCACTCTCAACCTTAGGGTTAGTTGTGGAGCTTCAATTCTTTACCTCAGATAATACTAAACTGTTCATA
GCTTGACTTGATTCAGTTTAATCATTTCACTGTTTCCCTATGGGATTGTTACAGACATGTTATTACCAGCC
TTATTGCTGTGTCAAACAAAAAGTCACAGCATGTTCCCTACCGAGATTCAAAATTGACATTTCTGCTGCAG
GTAATATGCACAGCTGAAGTGGTAGATTTCTCACGTTATGTTTTTGACATCTCTGATGTTAACTTTGTTTA
TTTATACATTTTCATCTCTTTCCAGGACTCACTTGGAGGTAACTCCAAGACCACTATAATTGCAAATATAA
GCCCATCTAGCTGGTAGACTTCTAAACACGATTTCTTTTTCCTTTTCTGCAAAAGGCTTGCTATAGTTACA
TGCATCTTACTGATATTTTAATTTGTATTTCTAGCTGTGCAGCTGAGACATTGAGCACATTAAAATTCGCG
CAACGGGCTAAGCACATACGGAATAATGTATGTCATGAACATGTCTTATTGACTTGTTTTTAATATGCAAA
ACAATAACTAATTGTTGTTTTTGTAGGCTATTATAAATGAGGATGCCTCTGGTGATGTGCTGAGCATGCGT
TTAGAGATCCAACATCTCAAGGTATAGATGATGAATTTCAATTTCGGTTTAATGAAAAATATTCTGTGCAC
TGGATTGCAATAAGTTCCAGGTTAACATGTTTCTTCTAATTATGGTCCTTTGTGCTATGATTGACGTTTGT
TGTTAATTAACAGTGGCCTGTGCCTGATATTTTTTGTTGCAGAGCGTTAATATGTTTTGTTGTACACAATC
TAATGCTTTGCTATTACCACAGAAAGAGCTTAGTCGCCTGCAAGGACAATCTGGATTTACTAACAATGGAT

FIG. 12B (con't)

TTGTCTGCGAGTCCCCTAGCGCATTCAAATGGGATCAAGCTAATGGCACATTCAGTCCACTTATGTTTGAT
AAGAGAGCTACACAGGTATTCATATACTGTTTTGTCTATATCGAACATTATCCATGTACTGGTTCTGTTTG
TTGAACTTATGTTTTTAACCGTATGCTTACTTTCTCTTTCTCGTGTTGTGTTCAGAGGAGAGATTATGATA
TTACACTTGCCGCTGCATTTAGGAGGGAGCAGGAAAAAGAAGCAAAGCTAAAGGCAGCAATTGCTGCAAAG
CAGATTGCCGAAGAGCTGGTATGCATCTCTCTTCACTACATTAGATTTTGTAGATACTCTAGAACACTTTG
TCACTAAAAAAGCAAATATATGCCAGTATAGTATTTTTTTTTCTTAATGTCAATTTGTTGTTGCACCACAG
GTGACTCAAAGATCAGAAGAGGTGAGAAGTTTCAGGATGAGGCTTCGCTTTCGTGAAGATCGAATCAAGAG
ATTGGAGCAAGTTGCATCGGGGAAGTTATCCGCTGAAGCACATCTCTTGCAAGAAAAGGAAGACCTCATGA
AGGAAATTGAAGCTCTACGGAACCAACTAGAACGAAATCCAGAAATTACAAGATTTGCTATGGAAAATCTA
CAACTGAAGGAGGAGATTCGAAGGTTAGCTTCGGTATCCAATCACTTCAGTTGCCCCCCTTTTCTACTGCC
TACACTAATATAGTTGGTAGCTTGATGCCTTTTTTTTTGAACTTGTAGGTTGCAGTCATTTGTTGATGAAG
GAGAATTGGAAAGAATGCATCAGCAGATAAATGTTTTAGAACATCAGGTATCCACTTTTGTGAAGGGGAAT
TTTTCAGTGATAAATTTTTTTTGTACTAAAATGAACTTTTTTTTACTCTTATAATTTTCTTAACATCCTGA
ACTTACTTAGTTTGTTTTCCTTTAGCTCCTAGAAGCACTTGACTGGAAACTTATGAATGAGAAGGATCCTG
TTAACAAGGTATGCTATATAATTTGTAGACTTCAATCCTGTTTAGTGAAAATATATGCAAAACTTTTGAAT
TTTCTTTAGCTAGCTGTTACAAATACTTGCATGGCATTATATCTCTTTACCTACCATTTTGCTTAGACGAT
ATCCCATAATGACTTCTACAGGACCTCTCACTATTTGGGGAGGAAGCTGGTGATGAGAAAAACGAGTTTCT
TCTTGTGCAGGTTGGTATTGTAGAACTATATTTGGCATATCGTCTGATGATATCTTCACAGATCTTTTAAA
ACAACCTGTAAATTAATCATAAGTGTACATTGTTGATCAACTCCGATACGGAGGAGGTAGCTGACTTAATA
AGTATCCTATTCTGATTCATTTTTTTCTGTAACATCAGTTTGTAATGTTGTTATACAGGCTATCCAAAATG
AGAGAGAAATCGAGTCACTACGTAAAAATTTGAGCGTCTGTCTTCAAGCAAAAGAGAAACTCGAGAGGTAT
ATCACTATTTCTTGTCTGTGTATTCTGTTATTGCATGCTATGGTTGTGTGGTATGATGAGAAAGGAATATC
ACTATTTCTTGTCTGTGTATTCTGTTATTGCATGCTATGGTTGTGTGGTATGATGAGAAAGGAATATTAAT
GTCATCAGCTTTTGCAATCATAATTAGTTCCTTAAATTTACAGTATTTACTTCAGGCCCCATGGTAACACA
ACTCTCACATATGTAAAACCCTTGGTGCCCCACAAACAAGATTAGAGGTGTATAGTATCTAGAAGTAAAAA
AACACTTTGTTGTTAGTGTTTCAAGTCACTGTAACTGCAGAAATTGTTGTGCTGTTTTTGCGCGCTACATT
TCAAGACCTACCATTTGGTTCTTGGTGTTCTTCTTGTTGTTGTTTTTTATTCTCCTTAGGAACGAAGCCTA
TAATAGTTGGTGGGAGGTCACCCAGGTTTGAGTTCCCCTCAACCTGAATCTGGGTGCTTATCTCTCCATCA
CTGAAAAGTTTCTTAGTTCCTTCCAGGCAATCTAGTATTTTTTTCTGCTTGGTAGTACTGTGCATATCGAA
TGGATAATATGCTTAGAATAGTTGGTGGGAGGTCACCCAGGTTTTGAGATATCAATTATTTAGTGGTTGGA
GTTAATGATGCATTTGTGCAAGTTCAAGAAAAGGTGTGCTTCTCAGAAGGGGTGATGGCTAGCGTAGGTGT
AGATCAACCACAACAACTCATCTGTGCTGCATTTTGTTTGATTTACTTGCATATGATATCCCAAGAATTAT
AAAAAGGCCCTAAAGAGTATGGCAAGTCATTTCTAAATCATCTTGGTTTGCAAGCTTCACTGATGGTTTTC
ACTGCATACTATTTTGTGTGTCCGGAATTATGTTCCTTTTTTTTGCTTTGTCTTGTCCAGAGATTTATGTG
GTTCATTTCTCACATTGGATGTTGTGCAGGCGTGTTGATGATTTGACTGTGGAGTTGGAGGTAGCGAAGAA
ATGCGACCATGAGAACAAAGAATTTAAGGCTGCACAGCACCAGGAACAGTCCGTCTTGCTTGATGCTCAGA
CAGAACTTAAGACATTGGTAGATGCAATAGCAACTGCAAGTCAAAGAGAAGCAGAAGCTCATGAAACTGCA
ATTGGGTTGGCCAAAGAGAATGAGAAATTGAGAACAGAGCTTACGACCCTGATCGAGGATAACAAGAGACT
GGTTGATCTCTATGAACAGGCTATTGTCAACATTGAGGTGAAACAACATGGAAATTATCCTTCCATTCCTC
AAACTGAAGATTCGAATGAGCAGCAGAGCAGCCATCCTTCTAATGGAGGGAATAGCCTGCTGGATGACCAA
CCAGAGGGTGCATATGGTTCACGTAGTGATGCTGTAGAAGAGCCTATGATAGTGGATGAAAACTGCAGCCA
CAAGGATGACCCTTCGAGATCTGAATtTTCAGAACTGCAGCTTCAACTGGAAGAGATGCATGAAGAAAATG
ATAAACTTATGAGTTTGTATGAGAAAGCAATGCAAGAAAGGGATGAATTTAAAAGGAAATTTTCTGAGCAA
AGCAATCATGAAACCACAGAAGACGTTCAGTTCAGAGATGCTGAAATGGATGAAGCAATGGATACCATGCA
AAGCAATCCTGAAACTACAGAAGACATTCAGTTCAGAGATGCTGAAATGGATAGTATGCTAAGCAATCTTG
AAAGTTCAGAAGACATTCAGTTCAGAGATGCTGAAACCGATGCTGAGGGTTTCCAAGGAGAGCATGTACAT
GACTCTCCAATTGTAGCTTTCAAAGAAGCGATGCAGCTTGTCCGTGTCAAGCTGGAGCATGTCCAAGACAA
GCTTGTGACTGCCCAGGATGCAGTGCAATATTTCAAGCTACTTGAAATGGCTAGCACCAAGGCAGAAGAAC
TTTCATCAAGCATTCAGCTCTGCTGTCTAGATGTCCAGAAAGAGCAGGAAGACATCAACGCCCTCAAGTCC
GCACTGTCAATATCACACGAGAGAGAAAACGCTTTGGAAGGCAAGTTTTTCTCGCCTGTGGCATCATGCCG

FIG. 12B (con't)

GGACTTGCATTTGAAAACCGAAGCCCTTGCCGGGTCCAAGTTTGGCGTCAATGTTCAATCAATGAATAAAA
AGATGGAGCAGTTGAGTAGGTTGAGAACTCGCAAAACCGAGATTTCCGCTGCACGTGCAGAGGCACGCAGG
TCTGAAACCGAGCTGAGAAACAAAATCGATGGCCTTAAACAGAAATACCGTTCCTTCGAGGCCCAAAGGAA
GGAGACAGAAAGGGTTCTCTTCGCCATCGACAACCTGGAGTGCCCCGCGACTCCGTTGCAGAAGCCCATGA
ATTTCGGCAAGGCGTCGGAGCTGCTGAAGTCCGAGGAGGAGAGGACAAAGCTCTTGTCTGAACTGAAGAAG
TTCCGCGAGCAGCTTAGCGTGGTGCAGAAGGAGATCAAGAGCATGAGGAACTGCGACGACATCGACGGTGA
GATGTCGCGCCTTGAATCGGAGATGGAGGGCTGCTTCCTCTCCCTGCTGGAAGCCGAGACCGAGAAGTTTG
TGCGGGATCACACCTTGGCCGAAGTCTGGGAGGTTCAGCAGAAGGACTTGCCGAGCCTACTGGTCGACTAC
CAGGACAGCGTTTTCCATGTGAAGCTGGAGGAGGAGCAGATCAGGGTGTGCGAGGCGTCGTTGCAGCACCA
GACGACGTCCCTGGACGAGATGAACTCGAAGCTGAGCCAGGCGATGCGGGACCTCGGCGAGCTTCTGGTTG
CCAGAGGTTTGGACGCCTCCACGCCGCACGTCTCCGACAAGGTGAAGGGGGACCTCGACGCCATCGAGGCC
CATGTCGCCGAGGCCAGGCAGCTCTTGCTCGTCGACAACCAATAAGATTTGCTGCGAACCAAAGCAAACCG
GTTCTCGCCATTGACAGACAGGCTGGTCTGTCTCCGCCTTCATTTTGTACAAATTCTTTGTAACGGAACGT
TGGTTCTCTCGGGTGCTGTTATCTGTGATTCGATTCTGTAGTTTGGATGGATGGGTGGATGTAGGTCCTGA
AGTGGACTGTAATAACTGTTCTGCGCGGCCTCTTGTTCTGTTCTCTGGTGGTCTGGCATCGAAGCTTCTTC
CAGAAGGCCGTTGCTAAGCTATGCAACTATAGATTCACCTCCTTCTGGTATGCACTTGGCCGTGCAAGACA
GCAATGATTGGACAATGTCGATTTCAAGAGGGCTTGACTATTTTGTTGTTTATCATAATCTGTGGCAGCGA
GCGTGGTTGCGTGTGTTCGTGAAGAAAAGAATGCCGGTGTTTCAGTTCATCGCAGGAGGTTGCAGGCCGAG
AAACTTGTTTTCCATTATTGTACTACTACATTTGGTGTTAACTTGGGCTGTGTCGTGGCGGTTGAGAAATG
TGTTCTGCAGGTCCTTGAGGGCATTAGGGCAGGTACAACGGTGTCCAGTCAGCTGTCTGGAAGGGGTGACA
GCTAGGATTTTAGATGATGTGGAGGAGAGAGAACAAAGAAAGAGAAACAACCCGTCTGTAGAATAACCAAC
GATCTGCAGCCCTTAAAATCCGGTGGATACAGATGGCCTTCTACCGTTGTATGGGGTGCCGTCTGCAAAGT
TGTTTGTAACTGCCTCCTTTGTCCCTGGATTAGTCTTCCACTCATCAATATTTGAGAGTGCTATAGACAGT
AAAATAGACGGTCTAATGTATAGGGTGTCTTAATCTCTGTCTATACGTGACGTGGAGCATCGTTACAGACA
ACGAGTTGTCTGAACTAATGTACATGCCCTCATGCTCCATGCTGCCGCCCGGTTCGGTTGTTTGGATTGCT
TCTGGAAGCTCCTTGAGCTATTTTTGTCTCTTCAGGGTTGCTTCTTTGCCTCTTTGTGTCCACTTGTTTGG
TTGGACTGCTCGGCTCGCCTATTTGGTCGTTGTTTTC (SEQ ID NO: 20)

FIG. 13A

AGAGCTCGGGGCTGGGCGGTTCGGTAAGAGAGGGAGAAGAACAAGGTCAGGGCCTTCTGGATCGCTAGGAG
GGGGATAGAGAGATTTTTCAGGCGAAATTGGTGCGGGACTGTTAAAATGGGGATGACATAGATTAAGAGAA
AGAAGAAGATGAATATGACACATGGACCCGCGTAGTTAGCGACATTAGCGTGTGATCCCGCTCAGGATTTT
CCTTTTCACTATGCGCCAAACATGTATTTAGCAGAAATCAACAGGAATAGACCGGGATTAAAGAGTATAGG
GTGACAGTTTCAGAGATTTATAAGTCAGGGTTTAACTCGAAGTGAGAGTACGAATTCAAGGTTTATTTCAT
ACTTTAGTGGTGCTTGCAATCCTCATGACAACTAAATTTGCCAATGTGGTACAAATTAGTTCATGTATTTA
ATTAACATATCTTGTGCACTCACCAATGTGGTTTCTCAATTGTTCACTTTGTTTCATATCTACTTTATGGC
ATGAAAATTTTGATGTCATTGTAAAAAAGAACTCTAGCCGAAGATAGAGATGCAACTCTTCAATCTTAAGG
AGTAAGGGTGTTGTGAGAACCGGGTGAACCGGGTGCTAACTCAATGGCCTGAGTTTGTAGTGGCAAAGCCA
TGCACTCTCTTCGAGTCTATACAGTAGACTCCGTTGGGGTGCGATCCGTGTTAAATTGCACAAATATCTCA
TCACATATTTACATAACATCCGGTTAAGTTTTTGCCAATGTTCAGGACTAAGGCTGCTAAAGACAATTTG
AATAAAAACCATGAACAAGTAGCAGTTTACTGGTTAGAACGCCAATTTTTTGGCTTCAGCCCCGAGGTGTA
TGGATGTTGAAAAACAAGTTTGACTGAAAACAGCTCGGTCCAAGAGCAAGAGTGTTCAAAATAATTTTATA
CAAAAAAAAAAGTTCCGGATAGCAAACCCATCAAGAGTTCATTTTCCTTCAGTGGTACCAACCGGAGGGTG
GAAAATAGTGCAAAATACCACTCGTATTAACTAAACAAACAGCTTGTTTCCGAATCATTTGAACAAAAAAC
TGTAAAAATCGACCAAAAAACAAAAATAACGCGCCAGGTAGGGGTCGAACCTACGGCCTTCCGCTTAGGAA
ACGGACGCTCTATCCACTGAGCTACAGGCGCCTTGTTGTATGAGATGCAACGGAACCATTTTACAACAATC
GCGTAGTAGATGCATCTACGGAAGCTTATTTGGACGGAGCACAAACCCTTCTCGAAGTCTACTAGAAACAC
CGGAAGCGGCGGCGGGGACAGCACAGGGAAGGAAAAGAAGCCAAGAGGCGGCGCCGCCGATCCACCCAGAC
CGAGAGCACCTTGGCCGACGGCATGGCGCTGCTGATGGAGCCCGGGTCGGAGCCCCTGACGGAGGGCGAGA
AGGCCGACCTGGACGCCATCGCCGCCATCAAGGAGTCGGCGGCGCGCGAGTACAGGGAGGAGGGCAACCAG
TTCGTCAAGAAGGGCCGGAAGCACTACCCCGACGCCGTCGACTGCTACACCAAGGCCATCGCCCAGATGGG
CGCCCTCTCCGCCCCGAACCCCGACGCCTCCGTCCTCTTCGCCAACCGCGCGCACGTCAACCTCCTCCTCG
GCAACCACCGCCGCGCCCTCGACGACGCCCAGCAGGCCGTCCGCCTCTCCCCCTCCAACCTCAAGGTCCGC
ACGCTCGCTCGCTCTAGATTACGCCTCTCTTGCTCCAATTTCTCGGATTTGGCGAGGAAGCCGCCGTGTGA
TGTGTGACATTCGTGTAGCCAGGCGCACTACCGGGCGGCGAAGGCCGCGCTTGCTCTCGACCAGTTGCCCC
AGGCGGCGTCCTTCTGCCGGCGGGGGCTCGAGCAGGACCCCGCCAACGAGGAGCTCAAGAAATTCCTCGCG
CAGGTGGAGGCGCAGCAGCGCGAGCGGGATCTTAAAAGGGCCAAGGTTGAACAGGCCATATCCGCCGCGAA
GGTCTCTTCTGTTCCAAATTGGCAGTTGAGCATTTCCTTATTCTTTTCCTGTTTGTGTAATTGACTGTATT
AGATGCATATAGGATCTTGCTGCTGCTATAGAGAAGAGAGGGCTGAGGCTGGGGAAGGCAGCATATCAGGA
GCTGACCGGGGTAAAGAAGCCGAAGCTGGATGAGCAGGGCGTGCTCCACTGGTCAGTTCTTCTGCTCTACC
CGGAGTCATGTCGAGCGACTTTATTGAGGATTTTCCGGAGACTGATATGTTCTCGGATCACCTTGATCTCA
TATCCTTGGAAAGTTACGTGATACTTTTTCTGATAGTATGTACATGAATATGCATAGATACTTTCATCACA
AAAAGGAGGAGGAATGGTTTCTTGAATTCCTGTTATCCTTAATTATCAAACATGTTCTCAGAAAGTTCTCC
ACCTTTGCCATGGGATGAGAACCACGCTTACACAAGGGACGCTATTGAGTTGTATTGTCAGGTTTGTTTAC
ACACTTCGAATTTTAATTGAGGGTTAACCTGTAAGGCTACCTTCTGCAAAGTGCTAGCGCCCACAGATGAT
CAAATTTTCTCTATCTAAATTTCACGAGGCATGAGTCACAACCTCTTCATACAACATGAAAACAAAACATT
CATGCCCCTGTGATGTGTATATACTACACACATTGTCCTTCTGATTTATTTTTCCACTAGATGATTGTGGG
CCAAGTTTTTTCGATCCAGACCTTTTTGTGATACTAAATTTTGGGGAATGCAACATAAGTTATGCTATTGC
TACTTAAGTGTTATTAGTAATTTCATTTGTCCGGTGCTAGAATGTCAAGATGGTAGCTCTAGCCTTTGTGG
CCACATTCTGAAAATTGTAGGATTATCCTTTACCAATTTTACAAGTGGCAGACTCATGTGAGAAAACTAGG
AGCTATTGAAAATTCAGATTTCAATGTGATCATTTTGATCATCGTTAGCAGCAGCATCCAGTCCAGTTTTT
GAAGTTATCTTCAAATTTAACAAATCTGTAGGATGGTTGCTCCTTCATTTACAACTATTATATTATTACAG
TCGACATAACTGTCACTACTTGAGAGTTAATATATACCTTCTGCAAAGTGCTAGCACCTACAGATATCAGA
TTTTCTTCTAAATGGCATGAGGCAAGTGCCACGACCTCTTCATAGAACATTAAAACAGAACACTGATGCCT
CTGATGTGTATATGCTACAGACAATGTCTTTCTGATTTATTTTTCACTAGATGATTGTGAGACAAGTTTTT
TCGATCCATACCCTTTTGCTACTAAGTTTTGGGGGATGCAACATAAGTTATGTTATTGCTACACTGATGTA
GTTAAGTGTTGTTGTTGGTAAATGGTTTATCTGGCAATAGAATGTCGAGATGATAGCTCTAACCTCTGTGG
CAATATTCTGTAGCATTATCCTTTACCAATTTTAACAGTGTCGGACTCATGTGAGAAAACTCGGAGTTGTT
GACAATTAAGATTTCAGTACTATCATGTTGATCATCATTAGCATTATCCAGTCCAGTTTTGCAAGTTATCT

FIG. 13A (con't)

TGAAGTTTCACAAATCTGTAGGATTTTTGCTTTTTCATTCACAATTAGGATTACAGTCAACATACCATTGT
CAGTACTTTGACACAGCTTTAGGATAGAAAAACTTTCTAGTTTCATTTCGTTGCCTTGCTGGCTAACTGGT
ATTTCCATTTGATACACTAGGCTGGTGATGGCACGCCGTTCTCCAAAAGTGAAATGTTAAAATATCTTCTG
GAAGGCACTGTCGACTCAGGGTCACTCCCAGAAAGCCTTGATGGGGAAGATGGAGAACATGATACTGTGAA
GGGCAGCACAGCTATATCACCAAGTATGTAAAACATATTCCTTAGGTTATTTCTCTAAATTTACATGATGT
ACAGTAAAAAGACAGCACGATGTGAACTGTGATTCTGTCAATTTCAGTATGTAATACTCCCTCCGTTCCTA
AATATAAGTCTTTTAAGAGATTCTACTATAGACTACATACGGAGCAAAAAGAGTGAACTTATACTCTAAAA
GGTGTCTATATACATCCGAATGTAGTCTCCATAGTGGAATCTCTAAAAAGACTTATATGTAGGAACCGAGG
GAGTATATCCAATCTGCCATTAGCAGAACTACATTTACTGCAACATGCTATAATGCTGTTATGCTGCGCTG
ATAAGTAGTTTCCATTTCAATGTGTGCAGGCCAGGGTAAGTGGATCAAAGTAAGAGAAGGGAAAACTCTTC
AGGAAGCGCTGCAGCATAAAGACTACATCATCCCGGCAGTACCTGGTCCGTTCTTCAACCTGTGTATACTT
TGCATTCGTGCGTATAGAATGCTTGTCATTGTTCAGCGCAAATAAGAGCTTCCATTAATTCCTGCGTGCAG
TGTTCTTTGTGGTTTCAAGGAAATCCGCCTTCCATTCGAAGTTCAAGGCTGGGAATTGGTCTTTGCCGTAG
AGCTGCCGTGTAGTAGTTCAGTT (SEQ ID NO: 21)

FIG. 13B

AGAGCTCGGGGCTGGGCGGTTCGGTAAGAGAGGGAGAAGAACAAGGTCAGGGCCTTCTGGATCGCTAGGAG
GGGGATAGAGAGATTTTTCAGGCGAAATTGGTGCGGGACTGTTAAAATGGGGATGACATAGATTAAGAGAA
AGAAGAAGATGAATATGACACATGGACCCGCGTAGTTAGCGACATTAGCGTGTGATCCCGCTCAGGATTTT
CCTTTTCACTATGCGCCAAACATGTATTTAGCAGAAATCAACAGGAATAGACCGGGATTAAAGAGTATAGG
GTGACAGTTTCAGAGATTTATAAGTCAGGGTTTAACTCGAAGTGAGAGTACGAATTCAAGGTTTATTTCAT
ACTTTAGTGGTGCTTGCAATCCTCATGACAACTAAATTTGCCAATGTGGTACAAATTAGTTCATGTATTTA
ATTAACATATCTTGTGCACTCACCAATGTGGTTTCTCAATTGTTCACTTTGTTTCATATCTACTTTATGGC
ATGAAAATTTTGATGTCATTGTAAAAAAGAACTCTAGCCGAAGATAGAGATGCAACTCTTCAATCTTAAGG
AGTAAGGGTGTTGTGAGAACCGGGTGCTAACTCAATGGCCTGAGTTTGTAGTGGCAAAGCCATGCACTCTC
TTCGAGTCTATACAGTAGACTCCGTTGGGGTGCGATCCGTGTTAAATTGCACAAATATCTCATCACATATt
TACATAACATCCGGTTAAGTTTTTTGCCAATGTTCAGGACTAAGGCTGCTAAAGACAATTTGAATAAAAAC
CATGAACAAGTAGCAGTTTACTGGTTAGAACGCCAATTTTTTGGCTTCAGCCCCGAGGTGTATGGATGTTG
AAAAACAAGTTTGACTGAAAACAGCTCGGTCCAAGAGCAAGAGTGTTCAAAATAATTTTATACAAAAAAAA
AAGTTCCGGATAGCAAACCCATCAAGAGTTCATTTTCCTTCAGTGGTACCAACCGGAGGGTGGAAAATAGT
GCAAAATACCACTCGTATTAACTAAACAAACAGCTTGTTTCCGAATCATTTGAACAAAAAACTGTAAAAAT
CGACCAAAAAACAAAAATAACGCGCCAGGTAGGGGTCGAACCTACGGCCTTCCGCTTAGGAAACGGACGCT
CTATCCACTGAGCTACAGGCGCCTTGTTGTATGAGATGCAACGGAACCATTTTACAACAATCGCGTAGTAG
ATGCATCTACGGAAGCTTATTTGGACGGAGCACAAACCCTTCTCGAAGTCTACTAGAAACACCGGAAGCGG
CGGCGGGGACAGCACAGGGAAGGAAAAGAAGCCAAGAGGCGGCGCCGCCGATCCACCCAGACCGAGAGCAC
CTTGGCCGACGGCATGGCGCTGCTGATGGAGCCCGGGTCGGAGCCCCTGACGGAGGGCGAGAAGGCCGACC
TGGACGCCATCGCCGCCATCAAGGAGTCGGCGGCGCGCGAGTACAGGGAGGAGGGCAACCAGTTCGTCAAG
AAGGGCCGGAAGCACTACCCCGACGCCGTCGACTGCTACACCAAGGCCATCGCCCAGATGGGCGCCCTCTC
CGCCCCGAACCCCGACGCCTCCGTCCTCTTCGCCAACCGCGCGCACGTCAACCTCCTCCTCGGCAACCACC
GCCGCGCCCTCGACGACGCCCAGCAGGCCGTCCGCCTCTCCCCCTCCAACCTCAAGGTCCGCACGCTCGCT
CGCTCTAGATTACGCCTCTCTTGCTCCAATTTCTCGGATTTGGCGAGGAAGCCGCCGTGTGATGTGTGACA
TTCGTGTAGCCAGGCGCACTACCGGGCGGCGAAGGCCGCGCTTGCTCTCGACCAGTTGCCCCAGGCGGCGT
CCTTCTGCCGGCGGGGGCTCGAGCAGGACCCCGCCAACGAGGAGCTCAAGAAATTCCTCGCGCAGGTGGAG
GCGCAGCAGCGCGAGCGGGATCTTAAAAGGGCCAAGGTTGAACAGGCCATATCCGCCGCGAAGGTCTCTTC
TGTTCCAAATTGGCAGTTGAGCATTTCCTTATTCTTTTCCTGTTTGTGTAATTGACTGTATTAGATGCATA
TAGGATCTTGCTGCTGCTATAGAGAAGAGAGGgCTGAGGCTGGGGAAGGCAGCATATCAGGAGCTGACCGG
GGTAAAGAAGCCGAAGCTGGATGAGCAGGGCGTGCTCCACTGGTCAGTTCTTCTGCTCTACCCGGAGTCAT
GTCGAGCGACTTTATTGAGGATTTTCCGGAGACTGATATGTTCTCGGATCACCTTGATCTCATATCCTTGG
AAAGTTACGTGATACTTTTTCTGATAGTATGTACATGAATATGCATAGATACTTTCATCACAAAAAGGAGG
AGGAATGGTTTCTTGAATTCCTGTTATCCTTAATTATCAAACATGTTCTCAGAAAGTTCTCCACCTTTGCC

FIG. 13B (con't)

ATGGGATGAGAACCACGCTTACACAAGGGACGCTATTGAGTTGTATTGTCAGGTTTGTTTACACACTTCGA
ATTTTAATTGAGGGTTAACCTGTAAGGCTACCTTCTGCAAAGTGCTAGCGCCCACAGATGATCAAATTTTC
TCTATCTAAATTTCACGAGGCATGAGTCACAACCTCTTCATACAACATGAAAACAAAACATTCATGCCCCT
GTGATGTGTATATACTACACACATTGTCCTTCTGATTTATTTTTCCACTAGATGATTGTGGCCAAGTTTT
TTCGATCCAGACCTTTTTGTGATACTAAATTTTGGGGAATGCAACATAAGTTATGCTATTGCTACTTAAGT
GTTATTAGTAATTTCATTTGTCCGGTGCTAGAATGTCAAGATGGTAGCTCTAGCCTTTGTGGCCACATTCT
GAAAATTGTAGGATTATCCTTTACCAATTTTACAAGTGGCAGACTCATGTGAGAAAACTAGGAGCTATTGA
AAATTCAGATTTCAATGTGATCATTTTGATCATCGTTAGCAGCAGCATCCAGTCCAGTTTTTGAAGTTATC
TTCAAATTTAACAAATCTGTAGGATGGTTGCTCCTTCATTTACAACTATTATATTATTACAGTCGACATAA
CTGTCACTACTTGAGAGTTAATATATACCTTCTGCAAAGTGCTAGCACCTACAGATATCAGATTTTCTTCT
AAATGGCATGAGGCAAGTGCCACGACCTCtTCATAGAACAtTAAAACAGAACACTGATGCCTCTGATGTGT
ATATGCTACAGACAATGTCTTTCTGATTTATTTTTCACTAGATGATTGTGAGACAAGTTTTTTCGATCCAT
ACCCTTTTGCTACTAAGTTTTGGGGGATGCAACATAAGTTATGTTATTGCTACACTGATGTAGTTAAGTGT
TGTTGTTGGTAAATGGTTTATCTGGCAATAGAATGTCGAGATGATAGCTCTAACCTCTGTGGCAATATTCT
GTAGCATTATCCTTTACCAATTTTAACAGTGTCGGACTCATGTGAGAAAACTCGGAGTTGTTGACAATTAA
GATTTCAGTACTATCATGTTGATCATCATTAGCATTATCCAGTCCAGTTTTGCAAGTTATCTTGAAGTTTC
ACAAATCTGTAGGATTTTTGCTTTTTCATTCACAATTAGGATTACAGTCAACATACCATTGTCAGTACTTT
GACACAGCTTTAGGATAGAAAAACTTTCTAGTTTCATTTCGTTGCCTTGCTGGCTAACTGGTATTTCCATT
TGATACACTAGGCTGGTGATGGCACGCCGTTCTCCAAAAGTGAAATGTTAAAATATCTTCTGGAAGGCACT
GTCGACTCAGGGTCACTCCCAGAAAGCCTTGATGGGGAAGATGGAGAACATGATACTGTGAAGGGCAGCAC
AGCTATATCACCAAGTATGTAAAACATATTCCTTAGGTTATTTCTCTAAATTTACATGATGTACAGTAAAA
AGACAGCACGATGTGAACTGTGATTCTGTCAATTTCAGTATGTAATACTCCCTCCGTTCCTAAATATAAGT
CTTTTAAGAGATTCTACTATAGACTACATACGGAGCAAAAAGAGTGAACTTATACTCTAAAGGTGTCTAT
ATACATCCGAATGTAGTCTCCATAGTGGAATCTCTAAAAAGACTTATATGTAGGAACCGAGGGAGTATATC
CAATCTGCCATTAGCAGAACTACATTTACTGCAACATGCTATAATGCTGTTATGCTGCGCTGATAAGTAGT
TTCCATTTCAATGTGTGCAGGCCAGGGTAAGTGGATCAAAGTAAGAGAAGGGAAAACTCTTCAGGAAGCGC
TGCAGCATAAAGACTACATCATCCCGGCAGTACCTGGTCCGTTCTTCAACCTGTGTATACTTTGCATTCGT
GCGTATAGAATGCTTGTCATTGTTCAGCGCAAATAAGAGCTTCCATTAATTCCTGCGTGCAGTGTTCTTTG
TGGTTTCAAGGAAATCCGCCTTCCATTCGAAGTTCAAGGCTGGGAATTGGTCTTTGCCGTAGAGCTGCCGT
GTAGTAGTTCAGTT (SEQ ID NO: 22)

FIG. 14A

TGGCGAGCGGCGTCGGGCCGGAGGCGCGACGATGAAGGTGGTGGCCGCGGTGGACGCGAGCGAGGAGAGCC
TGCACGCGCTGTCGTGGGCGCTCGACAACGTCGTCCGGCCCCACCCCGGCGCGTCCCTCGTCGTCGTCCAC
GTCCAGCCGCGCGCCGACCACTTCGCCTACCCTGTCGCCGGGCACGGTACCGCCTGTCCTGTACAACAAGC
TAGCTCACACGCACACACACGTACGTACGCTCACGCTCACTGACGGAACTCGTTTGCGTGTGCATACGGAG
GCAGGCCTACAGTACGTCCCGCCCACGGCGGTGGACTCCGTGAGGAAGACGCACGAAGAGAACTCCCGGCG
AGTCGTGTCCGTCGCGCTCGACGTGTGCAGGCAGAAGCAGGTGAGCGCCACGGCGGCGGTGGTGGAGGGCG
ACGCCAAGGAGGCCATCTGCCGCGCCGTGGAGGACATGCACGCCGACCTCCTCGTCCTCGGCAGCCGCGGC
CTGGGCATGATCAAGAGGTACGCGCATGCCAATGAGATCACCACGCGTGAGCATCTTCGATAACAGATTGT
GATTCTGGGTGCAGTTCGACTACTTCACTGGCAGAGCCAAAAATACTAAAGCACAGCTTAGCTTTCTTCAG
TGTTCAAGCGACTTGAATTGCAAACATATGGAAATCCTTAAATTTCAAAATTTCAATGCTTGATTTGGTTG
GGGTTTGCCAGGTCCAGGCAGTAGTGCAACGCCTGGACGACACATGAGAGCCCTGGCAGCAAGCTACCGTG
ATGGGCTCTCCCCCATAAAAAATAAATTTAATATCGTTGTGGACACATGGTCCACATATCAGATATTAAAC
TGATAAGAACAGATACTACACTTGATCTTAGCCAAAAGGCCGAGAAAGGTATGAGTTGGAACATTGAGCTG
GGTCTTGTTTTATAGCCATCTTTCCCCAGGGTTTCTCCTCCGTCCGGGATGTGGTACTAAACCTGCTACTG
ACCTCTCTTCTATGCTCCGGCAATGCCACCCGCTGCTCGGTTGGGCCCAAACCGAGAGCCCGTAGCAGGCC
TTATCGAGTACGTCATGGGCTTTTCTGTTCCTGTTCCTTTTACCATTCTATATCTTGTAGTTTGCCTCCTG
TTGGGCTTGTCCCTATGGGCCTCCCCTTCTTATCCAGGCACATATTGAAATGCATGGCTGGCAAGAGGTGC
AATAGCTCGTTAAACTTGCCTCCTTAAACAGTAGTACATTTAAGAGAATCCAATGGGTAAAGAAAACACAG
TTGTTTCTTAGTTTTTCATGTTTATTTACTATGAGAGCAAGCCTTTATCACCGAGACAATAGTCATGTTGC
TTGCAGAGTTACAAGCATATGCATAATAAAACTCCATGGATCATCAAGCCACGCCTTGACCCTGTGCTTGT
GCTGGTGGTGTGTTGCAGGGCGTTGCTGGGCAGCGTGAGCGACTACCTCGCCCATCACGCCTCCTGCCCCG
TTCTCATCGTGAAGCCGCCCAGCAAGGCGCACCACAAGTGAAGCTCCAACTCTGCTGCCAGTGTCGACTGA
ATGTCTCGAGTGCCTCGTGCTTCCAATAAAGATGTGATCGAGCTCATGTGCAGTACTCTATGAACATCCTA
GAATGTAGGGAATAAACTGTTGTTTGGCCGCAAGCACTTGCTGAAATTTTTAATCTTGGTTAGTGCAGTTG
TTCCGATGCATTACATTGCCATGGACGTAGTGTTCTTTCTTCCTTGAAGTACAGAGTGCGGTGATGCTGCT
GAAAAACAGGCACATCTCGAAGAGTTCGGTTCGCCAAACACATGACCAGTACAAGACCTATTGATCACAAA
TACTCCATAATTCGCTCTAAAAAACGTATTCAGAATTCCTATTCATAATGCAGAGCATGAATGACCGTCGA
AGCATGTTCTGTTTCTAAGCAAGCATGCTTTTGTTTTAAAATGGAGACAAAAGTTTTGCCTCGTCTATTTA
ATGAAGAAGAGGGTAGAGTTCTGTATTACAAGGCCGCGAGGCCCACCCGCAATAAACATGGAATTACTCTC
CTGATAGAATGTTTCCCAAAATAACAAAATTGCATCTGCCAAGACCCAAAGCTTGGTCTAGTCTTTGATGG
CCTTGAGCAAGATGGTCTTCGGCTTGCTCTATTCTCGAAACACACGGGCATTTCTCTCGTTTCAAATGGTC
CAACTAATGAGCATTGTAAGCGACGCCATTGCTTTACAGTTGACCTTGTTGTTGCGGAAAGATTGACCCAC
CAATCTTTGTTGGGGCTCTTAAGGCGCCAAGAGGAGGTTCAAAGTT (SEQ ID NO: 23)

FIG. 14B

TGGCGAGCGGCGTCGGGCCGGAGGCGCGACGATGAAGGTGGTGGCCGCGGTGGACGCGAGCGAGGAGAGCC
TGCACGCGCTGTCGTGGGCGCTCGACAACGTCGTCCGGCCCCACCCCGGCGCGTCCCTCGTCGTCGTCCAC
GTCCAGCCGCGCGCCGACCACTTCGCCTACCCTGTCGCCGGGCACGGTACCGCCTGTCCTGTACAACAAGC
TAGCTCACACGCACACACACGTACGTACGCTCACGCTCACTGACGGAACTCGTTTGCGTGTGCATACGGAG
GCAGGCCTACAGTACGTCCCGCCCACGGCGGTGGACTCCGTGAGGAAGACGCACGAAGAGAACTCCCGGCG
AGTCGTGTCCGTCGCGCTCGACGTGTGCAGGCAGAAGCAGGTGAGCGCCACGGCGGCGGTGGTGGAGGGCG
ACGCCAAGGAGGCCATCTGCCGCGCCGTGGAGGACATGCACGCCGACCTCCTCGTCCTCGGCAGCCGCGGC
CTGGGCATGATCAAGAGGTACGCGCATGCCAATGAGATCACCACGCGTGAGCATCTTCGATAACAGATTGT
GATTCTGGGTGCAGTTCGACTACTTCACTGGCAGAGCCAAAAATACTAAAGCACAGCTTAGCTTTCTTCAG
TGTTCAAGCGACTTGAATTGCAAACATATGGAAATCCTTAAATTTCAAAATTTCAATGCTTGATTTGGTTG
GGGTTTGCCAGGTCCAGGCAGTAGTGCAACGCCTGGACGACACATGAGAGCCCTGGCAGCAAGCTACCGTG
ATGGGCTCTCCCCCATAAAAAATAAATTTAATATCGTTGTGGACACATGGTCCACATATCAGATATTAAAC
TGATAAGAACAGATACTACACTTGATCTTAGCCAAAAGGCCGAGAAAGGTATGAGTTGGAACATTGAGCTG
GGTCTCGTTTTATAGCCATCTTTCCCCAGGGTTTCTCCTCCGTCCGCGATGTGGTACTAAACCTGCTACTG

FIG. 14B (con't)

```
CCCTCTCTTCTATGCTCCGGCAATGCCACCCGCTGCTCGGTTGGGCCCAAACCGAGAGCCCGTAGCAGGCC
TTACCGAGTCACGTCATGGGCTTTTCTGTTCCTGTTCCTTTTTCCATTCTCTCTCTTGCAGCTTGCCTCCT
CTTCTGCTTTTCCCTTTGTGCCTTCCCTTCTTATCCTGGTAGCATATTGAAATGCATGGCTGGAAGATGTG
CAATAGCTAGTTAACTTGCCTCCTTAAACAGTAGTACATTTAAGAAAATCCAATGGCTAAAGAAAACACAG
TTGTTTTTTAGTTTTTCATGTTTATTTACTATGAGAGCAAGCCTTTATCACCGAGACAATAGTCATGTTGC
TTGCAGAGTTACAAGCATATGCATAATAAAACTCCATGGATCATCAAGCCACGCCTTGACCCTGTGCTTGT
GCTGGTGGTGTGTTGCAGGGCGTTGCTGGGCAGCGTGAGCGACTACCTCGCCCATCACGCCTCCTGCCCCG
TTCTCATCGTGAAGCCGCCCAGCAAGGCGCACCACAAGTGAAGCTCCAACTCTGCTGCCACTGTCGACTGA
ATGTCTCGAGTGCCTCGTGCTTCCAATAAAGATGTGATCGAGCTCATGTGCAGTACTCTATGAACATCCTA
GAATGTAGGGAATAAACTGTTGTTTGGCCGCAAGCACTTGCTGAAATTTTTAATCTTGGTTAGTGCAGTTG
TTCCGATGCATTACATTGCCATGGACGTAGTGTTCTTTCTTCCTTGAAGTACAGAGTGCGGTGATGCTGCT
GAAAAACAGGCACATCTCGAAGAGTTCGGTTCGCCAAACACATGACCAGTACAAGACCTATTGATCACAAA
TACTCCATAATTCGCTCTAAAAAACGTATTCAGAATTCCTATTCATAATGCAGAGCATGAATGACCGTCGA
AGCATGTTCTGTTTCTAAGCAAGCATGCTTTTGTTTTAAAATGGAGACAAAAGTTTTGCCTCGTCTATTTA
ATGAAGAAGAGGGTAGAGTTCTGTATTACAAGGCCGCGAGGCCCACCCGCAATAAACATGGAATTACTCTC
CTGATAGAATGTTTCCCAAAATAACAAAATTGCATCTGCCAAGACCCAAAGCTTGGTCTAGTCTTTGATGG
CCTTGAGCAAGATGGTCTTCGGCTTGCTCTATTCTCGAAACACACGGGCATTTCTCTCGTTTCAAATGGTC
CAACTAATGAGCATTGTAAGCGACGCCATTGCTTTACAGTTGACCTTGTTGTTGCGGAAAGATTGACCCAC
CAATCTTTGTTGGGGCTCTTAAGGCGCCAAGAGGAGGTTCAAAGTT          (SEQ ID NO: 24)
```

FIG. 15A

A.
GCTTCTCCTGGAAGCTGCCGCGGACGTGGGTCAGGTCGGTCGACCAGCTGCCCATGAATTACGGCGACAAG
CTCTACGACCCGCTCTTCCCCTTCGGCTTCGGCCTCACCACCAAGCCGGCGGCGGATAGCAGGTAGCTAGG
AGTCTGAGTTTCTTTTCCTGCCCTAGTTAGTGTGCGATTAATTAGTGAGTCCGTGAGTAGTGAGAATCGGA
AATAAATGAGGAGGATATGGTTTTGATTGCGTCGCCCTGTAACTGTAAGTTCGCTACGAACATCCGATGAA
CTTGAAATCAATCTATATATAGTGCTGTCGGAATTCAGTCTATCTTAATTCTCGACTTCTCGAGTCGGTT
(SEQ ID NO: 25)

FIG. 15B

GCTTCTCCTGGAAGCTGCCGCGGACGTGGGTCAGGTCGGTCGACCAGCTGCCCATGAATTACGGCGACAAG
CTCTACGACCCGCTCTTCCCCTTCGGCTTCGGCCTCACCACCAAGCCGGCGGCGGATAGCAGCTAGCTAGG
AGTCTGAGTTTCTTTTCCTGCCCTAGTTAGTGTGCGATTAATTAGTGAGTCCGTGAGTAGTGAGAATCGGA
AATAAATGAGGAGGATATGGTTTTGATTGCGTCGCCCTGTAACTGTAAGTTCGCTACGAACATCCGATGAA
CTTGAAATCAATCTATATATAGTGCTGTCGGAATTCAGTCTATCTTAATTCTCGACTTCTCGAGTCGGTT
(SEQ ID NO: 26)

FIG. 16A

CAAACAGCCGTGACACACAAGAGGTACACTTTCTGAAAACTTCCGTCAATAACTACTTATTTTGGGTGGTG
ATTTCATGAAGAGGCCATGGCCCACCAGGGCTAATGTTAATACTTTGTATGTTCCTTTAAATAATGATGAT
GATGTATCTTGCTTTTTTAAGGACACATATTTTAAATATGGTTTATCAGGTGCCTTCCCCAGTTAATAAAA
CAGTGGAACCTATAAATTT
(SEQ ID NO: 27)

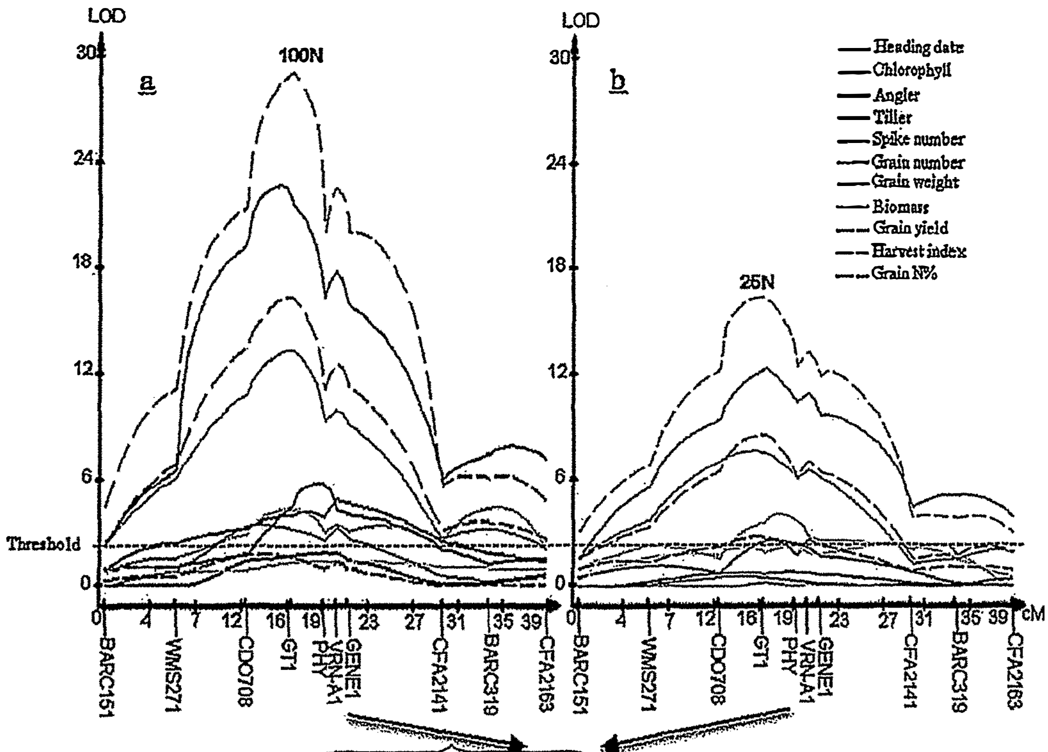
FIG. 16B

CAAACAGCCGTGACACACAAGAGGTACACTTTCTGAAAACTTCCGTCAATAACTACTTATTTTGGGTGGTG
ATTTCATGAAGAGGCGAATGTTAATACTTTGTATGTTCCTTTAGATAATGATGATGATGTAGCTTGCTTTT
TTAAGGACGCATATTTTAGATATGGTTTATCAAGTGCCTTCCCCAGTTAATATAACAGTGGAACCTAGAAA
TTTGTTTCTCCATTATTGTCATGCG
(SEQ ID NO: 28)

Plant ID#	V1G1	PCS		CYHS	AGLG	VRN-A1	Pheno		CYS	PHY		GT		STR	KIN		CBP		USPC3	MET		EX1	AMT		CDO708	BC1F2:3			BC1F3			Parents
																										A	B	H	A	B	H	
D1052	H	H	X	B	B	B	B		B	B		B		B	B		B		B	B		B	B		B	182	203	194				
P55	A	A	X	H	H	H	H		H	H		H		H	H		H		H	H		H	H		H				159	193	-	
D695	H	H		H	H	H	H	X	A	A		A		A	A		A		A	A		A	A		A	174	203	193				
T657	H	H		H	H	H	H		H	H	X	B		B	B		B		B	B		B	B		B	157	191	172	143	212	-	
B562	H	H		H	H	H	H		H	H	X	B		B	B		B		B	B		B	B		B	144	170	152				
D594	B	B		B	B	B	B		B	B	X	H		H	H		H		H	H		H	H		H	187	199	200				
D731	B	B		B	B	B	B		B	B	X	H		H	H		H		H	H		H	H		H	178	179	175				
D1061	A	A		A	A	A	A		A	A	X	H		H	H		H		H	H		H	H		H	159	163	157				
L447	H	H		H	H	H	H		H	H		H	X	A	A		A		A	A		A	A		A	158	181	161	168	206	-	
A210	A	A		A	A	A	A		A	A		A		A	A	X	H		H	H		H	H		H	108	124	113				
T485	A	A		A	A	A	A		A	A		A		A	A	X	H		H	H		H	H		H	160	157	167				
T1013	A	A		A	A	A	A		A	A		A		A	A	X	H		H	H		H	H		H	160	163	160				
CAP7	B	B		B	B	B	B		B	B		B		B	B		B	X	A	A		A	A		A		189					
T722	A	A		A	A	A	A		A	A		A		A	A		A	X	H	H		H	H		H	133	138	140				
CAP6	A	A		A	A	A	A		A	A		A		A	A		A		A	A	X	B	B		B	145						
Jagger	A	A		A	A	A	A		A	A		A		A	A		A		A	A	A	A	A		A							155
2174	B	B		B	B	B	B		B	B		B		B	B		B		B	B	B	B	B		B							171
																										158.3	174	165				

Fig. 17

Fig. 18A



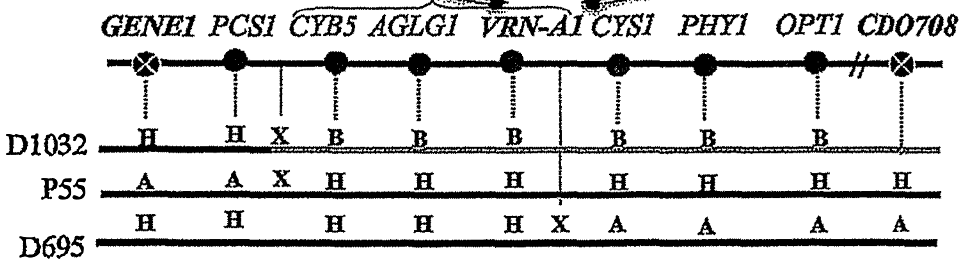


Fig. 18B

Fig. 19A Fig. 19B Fig. 19C

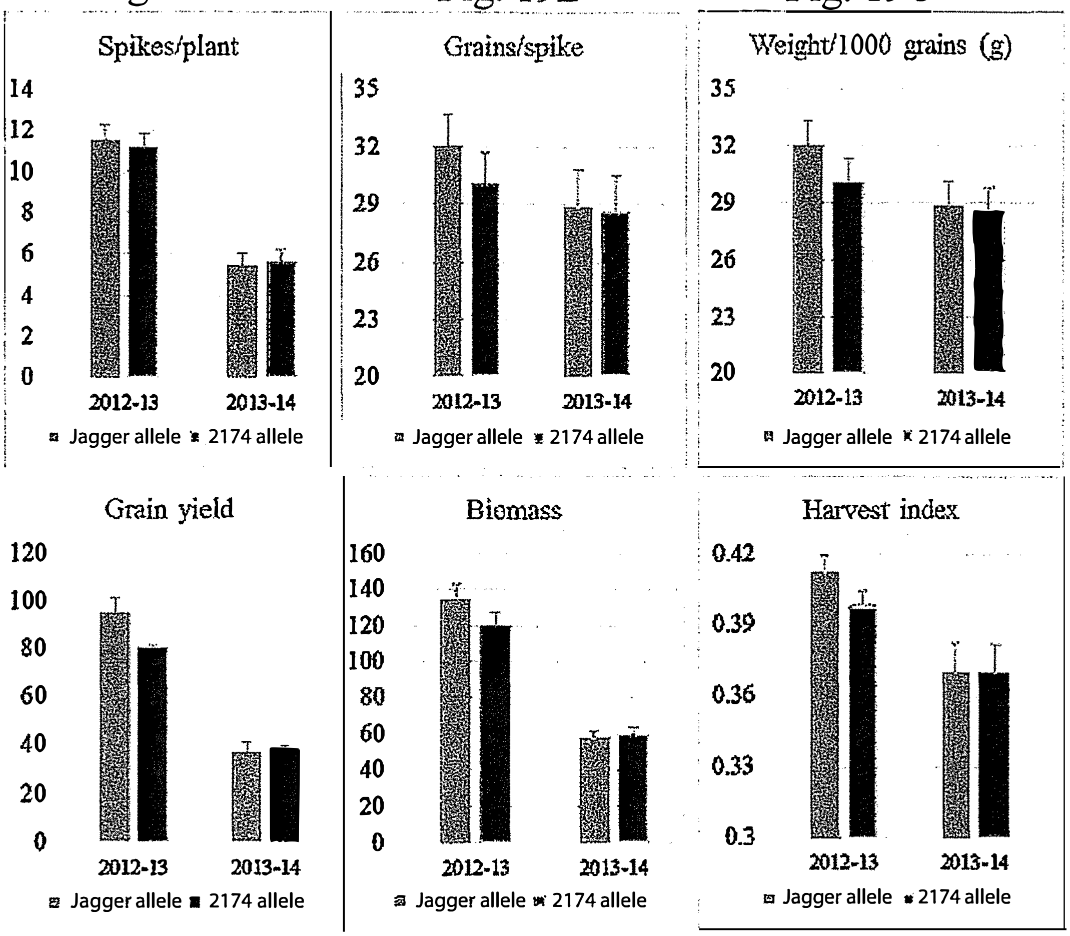


Fig. 19D Fig. 19E Fig. 19F

Fig. 20A

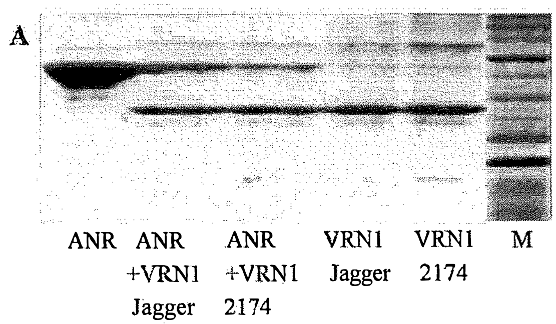


Fig. 20B

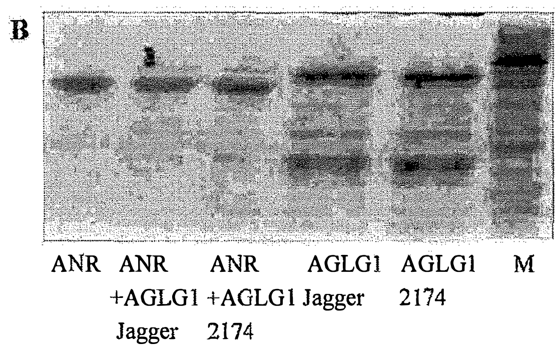


FIG. 21A

FIG. 21B

FIG. 21C

FIG. 21D

FIG. 21E

FIG. 21F

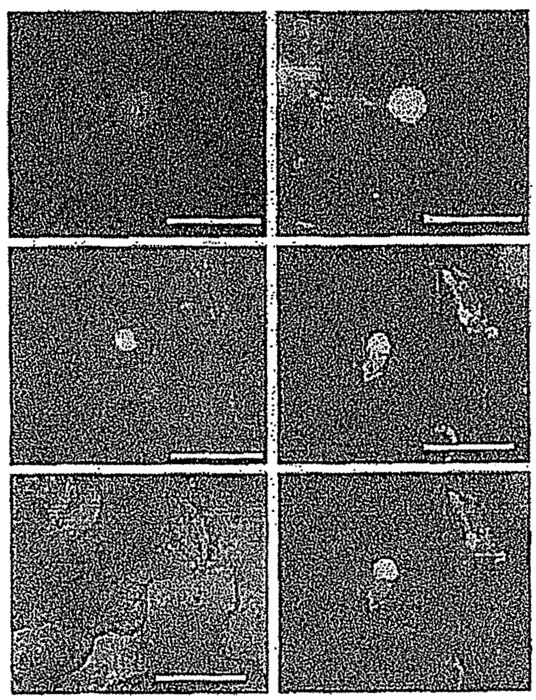


Fig. 22A

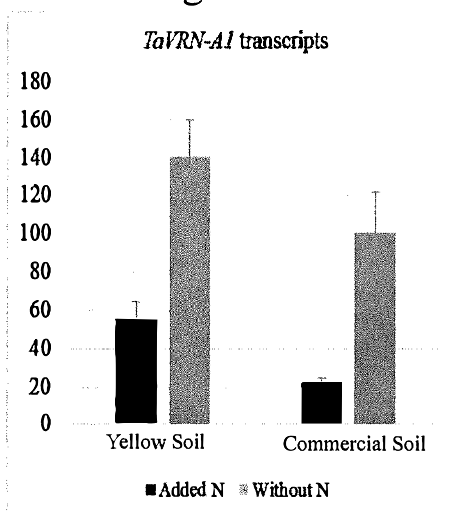


Fig. 22B

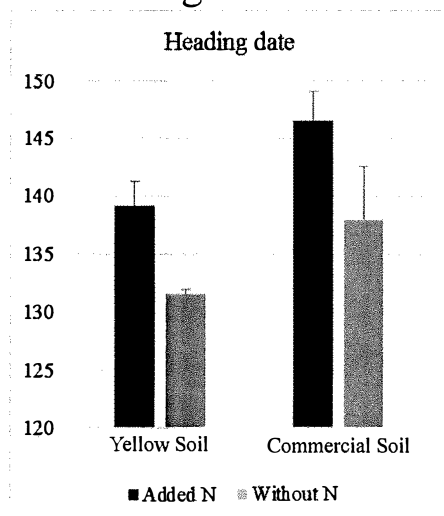


Fig. 22C

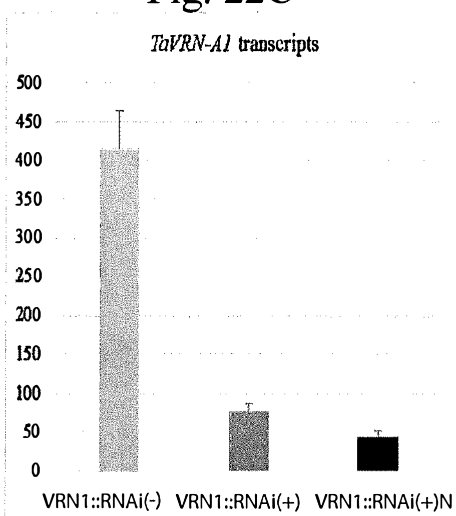


Fig. 22D

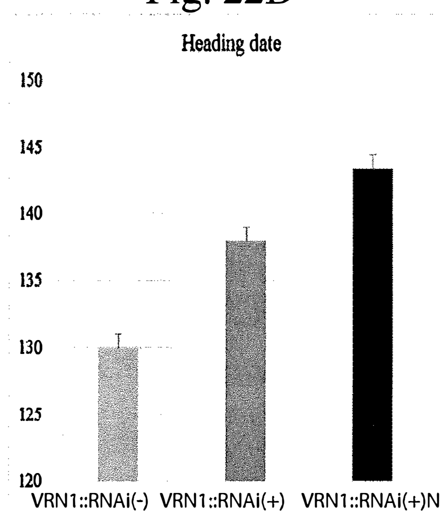


Fig. 23A

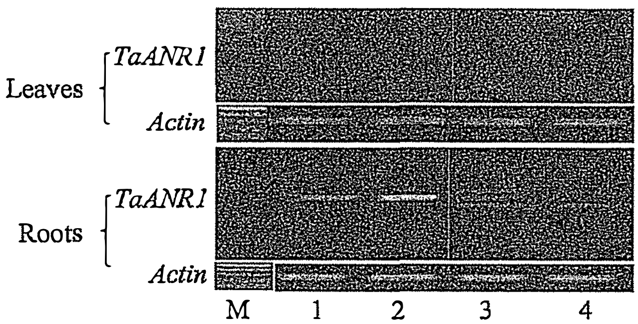


Fig. 23B

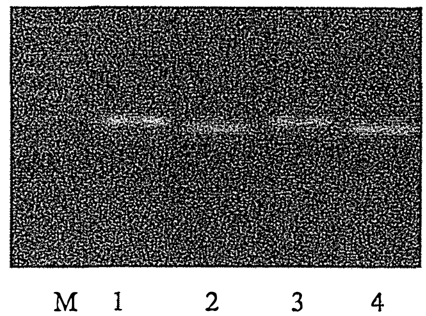


Fig. 23C

```
           Intron 5                                                                           Exon 6
TaANR-A1a GTACTACAACATTTACCAGCCTGAAACGTATGAAATATTTCAACAAACTGACTATTCATTTATTTGCAGGGGAGTCTTGTCCACCAAG
          |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||                       ||||||
TaANR-A1b GTACTACAACATTTACCAGCCTGAAACGTATGAAATATTTCAACAAACTGACTATTCAT-----------------------ACCAAG
```

Fig. 23D

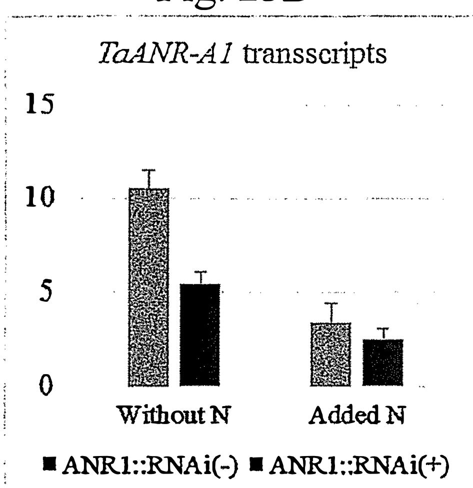
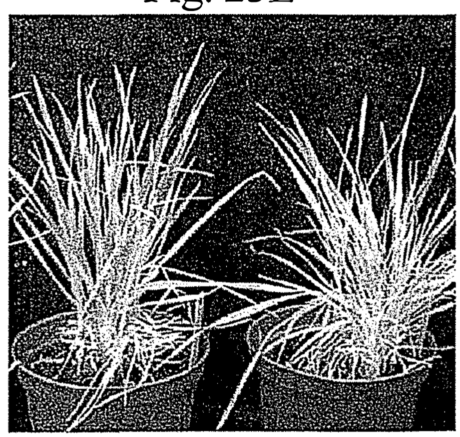


Fig. 23E



ANR1::RNAi(+) ANR1::RNAi(-)

FIG. 24

MGRGKVQLKRIENKINRQVTFSKRRSGLLKKAHEISVLCDAEVGLIIFSTKGKLYEFSTESCMDKILERY
ERYSYAEKVLVSSESEIQGNWCHEYRKLKAKVETIQKCQKHLMGEDLESLNLKELQQLEQQLESSLKHIR
SRKNQLMHESISELQKKERSLQEENKVLQKELVEKQKAHAAQQDQTQPQTSSSSSSFMLRDAPPAANTSI
HPAATGERAEDAAVQPQAPPRTGLPPWMVSHING (SEQ ID NO: 29)

FIG. 25A

MGRGKIVIRRIDNSTSRQVTFSKRRNGIFKKAKELGILCDAEVGLVIFSSTGRLYEYASSSMKSVIDRYG
RAKEEQQLVANPNSELKSWQREAASLRQQLHNLQENHRQLMGQDLSGMGVKELQALENQLEISLRCIRTK
KDQILIDEIHELNHKGSLVHQENMELYKKINLIRQENVELQKKLSETEAVTEVNRNSRTPYNFAVVEDAN
VSVDLELNSPQQQNDVEHTAPPKLGLQLHP (SEQ ID NO: 30)

FIG. 25B

ATGGGGCGCGGCAAGATAGTGATCCGGCGGATCGACAACTCCACGAGCCGGCAGGTGACGTTCTCGAAGC
GGAGGAACGGGATCTTCAAGAAGGCCGAGGAGCTGGGTATTCTCTGCGATGCCGAGGTCGGTCTCGTCAT
CTTCTCCAGCACCGGCCGCCTCTATGAGTACGCCAGCTCCAGCATGAAGTCAGTGATAGATCGATATGGC
CGAGCCAAGGAGGAGCAGCAACTTGTTGCAAACCCCAACTCGGAGCTTAAGTTCTGGCAAAGGGAGGCAG
CAAGCTTGAGACAACAACTGCACAACTTGCAAGAAAATCATCGGCAGTTGATGGGACAAGATCTTTCTGG
AATGGGTGTCAAGGAACTGCAGGCTCTAGAAAATCAACTGGAAATAAGTCTGCGTTGCATCCGGACAAAA
AAGGACCAAATCTTGATTGATGAGATTCATGAACTGAATCACAAGGGGAGTCTTGTCCACCAAGAAAACA
TGGAATTATACAAAAAGATTAACCTAATTCGTCAGGAAAATGTTGAGTTACAGAAAAAGCTCTCTGAGAC
GGAGGCAGTGACTGAAGTTAACCGAAATTCAAGAACTCCATACAATTTTGCAGTTGTTGAAGATGCCAAT
GTTTCTGTTGATCTTGAACTCAATTCCCCGCAGCAACAAAATGATGTTGAGCATACTGCGCCCCCTAAAC
TAGGATTGCAACTACATCCATGA (SEQ ID NO: 31)

FIG. 25C

MGRGKIVIRRIDNSTSRQVTFSKRRNGIFKKAKELGILCDAEVGLVIFSSTGRLYEYASSSMKS
VIDRYGRAKEEQQLVANPNSELKSWQREAASLRQQLHNLQENHRQLMGQDLSGMGVKELQALEN
QLEISLRCIRTKKDQILIDEIHELNHKLSETEAVTEVNRNSRTPYNFAVVEDANVSVDLELNSP
QQQNDVEHTAPPKLGLQLHP (SEQ ID NO: 34)

FIG. 25D

ATGGGGCGCGGCAAGATAGTGATCCGGCGGATCGACAACTCCACGAGCCGGCAGGTGACGTTCT
CGAAGCGGAGGAACGGGATCTTCAAGAAGGCCGAGGAGCTGGGTATTCTCTGCGATGCCGAGGT
CGGTCTCGTCATCTTCTCCAGCACCGGCCGCCTCTATGAGTACGCCAGCTCCAGCATGAAGTCA
GTGATAGATCGATATGGCCGAGCCAAGGAGGAGCAGCAACTTGTTGCAAACCCCAACTCGGAGC
TTAAGTTCTGGCAAAGGGAGGCAGCAAGCTTGAGACAACAACTGCACAACTTGCAAGAAAATCA
TCGGCAGTTGATGGGACAAGATCTTTCTGGAATGGGTGTCAAGGAACTGCAGGCTCTAGAAAAT
CAACTGGAAATAAGTCTGCGTTGCATCCGGACAAAAAAGGACCAAATCTTGATTGATGAGATTC
ATGAACTGAATCACAAGCTCTCTGAGACGGAGGCAGTGACTGAAGTTAACCGAAATTCAAGAAC
TCCATACAATTTTGCAGTTGTTGAAGATGCCAATGTTTCTGTTGATCTTGAACTCAATTCCCCG
CAGCAACAAAATGATGTTGAGCATACTGCGCCCCCTAAACTAGGATTGCAACTACATCCATGA
(SEQ ID NO: 35)

FIG. 26A

MESDCQFLLAPPPRMYAAPGDDGQFLQQQQQQLSGGGAGERKRRFTEEQVRSLESTFHTRRAKLDPREKA
ELARELGLQPRQVAIWFQNKRARWRSKQPEQDFAELRGHYDALRARVESLKQEKLTLAAQLEELKKKLDE
RQDQSASCGGSCAVADVDDKRDNVSSCVAAKDESAAPAADVSDGSTPGWYEYDDHLVYGVDLHEPFCATQ
ELWETSWPLVEWNAVA (SEQ ID NO: 32)

FIG. 26B

ATGGAGAGCGACTGCCAGTTCCTGCTGGCGCCGCCGCCGCGCATGTACGCCGCGCCGGGGGACGACGGCC
AGTTCCTTCAGCAGCAGCAGCAGCAGCTGAGCGGCGGCGGCGCCGGGGAGAGGAAGCGGCGGTTCACGGA
GGAGCAGGTGCGGTCGCTGGAGAGCACGTTCCACACGCGGCGCGCCAAGCTGGACCCCCGGGAGAAGGCG
GAGCTGGCGCGCGAGCTGGGGCTGCAGCCGCGCCAGGTGGCCATCTGGTTCCAGAACAAGCGCGCCCGGT
GGCGCTCCAAGCAGCCGGAGCAGGACTTCGCGGAGCTGCGCGGCCATTACGACGCCCTCCGCGCCCGCGT
CGAGTCGCTCAAGCAGGAAAAGCTCACTCTCGCCGCGCAGCTGGAAGAGCTGAAGAAGAAGCTGGACGAG
CGGCAAGACCAGAGCGCTAGCTGCGGCGGCTCTTGCGCCGTCGCCGACGTAGACGACAAGAGGGATAACG
TTAGCAGCTGCGTCGCGGCGAAGGATGAGAGCGCGGCGCCGGCGGCAGACGTGTCGGACGGCTCAACTCC
GGGCTGGTACGAGTATGACGACCACCTGGTGTATGGGGTTGACCTGCACGAGCCGTTCTGCGCCACTCAG
GAGCTGTGGGAGACGTCATGGCCGCTGGTGGAGTGGAACGCAGTGGCATGA(SEQ ID NO: 33)

ENHANCEMENT OF NITROGEN USE EFFICIENCY IN WHEAT AND OTHER PLANTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of co-pending application Ser. No. 13/892,403, filed May 13, 2013 entitled: "ENHANCEMENT OF NITROGEN USE EFFICIENCY IN WHEAT AND OTHER PLANTS", which is a continuation of abandoned application Ser. No. 13/841,201, filed Mar. 15, 2013, entitled "ENHANCEMENT OF NITROGEN USE EFFICIENCY IN WHEAT AND OTHER PLANTS", which application is a continuation-in-part of co-pending U.S. application Ser. No. 13/157,057 filed on Jun. 9, 2011 entitled, "ENHANCEMENT OF NITROGEN USE EFFICIENCY IN WHEAT AND OTHER PLANTS", which application claims the priority of U.S. Provisional Patent Application No. 61/352,979 entitled, "ENHANCEMENT OF NITROGEN USE EFFICIENCY IN WHEAT AND OTHER PLANTS," filed Jun. 9, 2010, and U.S. Provisional Patent Application No. 61/367,671 entitled, "ENHANCEMENT OF NITROGEN USE EFFICIENCY IN WHEAT AND OTHER PLANTS," filed Jul. 26, 2010, the contents of all five are hereby incorporated by reference.

FIELD OF THE INVENTION

The invention generally relates to the enhancement of the efficiency of nitrogen use in plants. In particular, the invention provides genes responsible for efficient use of nitrogen in plants, methods of using the genes to genetically engineer plants so that they use nitrogen more efficiently, and transgenic plants that are genetically engineered to contain and express such genes and thereby utilize nitrogen more efficiently. Identification of the genes also aids in carrying out suitable crosses for plant breeding in order to enhance the desired phenotype of efficient nitrogen utilization by progeny plants

BACKGROUND OF THE INVENTION

Nitrogen is One of the Most Important Nutrients in Crop Production.

Nitrogen (N) is an essential nutrient for growth and development and a major constituent of proteins, nucleic acids, and secondary metabolites in plants (Scheible 2004; Moose and Below 2009). Wheat is highly responsive to N fertilization, with significant amounts of supplemental N required to achieve maximal grain yields. A sevenfold increase in N fertilizer usage has been associated with a twofold increase in food production over the last four decades (Hirel et al. 2007; Shrawat et al. 2008). A further threefold increase in N input has been projected to meet food demands for main crops including wheat, rice and maize (Shrawat et al. 2008; Tilman et al. 2002), due to a projected increase in world population to 9 billion by 2050 (McMichael 2001). An estimated 12.5 million tons of N were applied to agriculture production in 2007 in the United States, and additional N fertilizer is needed to account for N removal in consumed forage in dual purpose wheat planted in the southern Great Plains (MacKown and Carver 2007).

Nitrogen Use Efficiency is One of the Most Effective Approaches to Sustainable Agriculture.

Although large amounts of N are applied to soils, only part of the N is taken up and utilized by plants in the year of application. For example, nitrogen use efficiency (NUE) in wheat is only about 30-35% (Raun and Johnson 1999; Tilman et al. 2002), and the remaining 65-70% (assuming fertilizer-soil equilibrium) is lost by gaseous plant emission, soil denitrification, surface runoff, volatilization, and leaching, which contributes to atmospheric greenhouse gases and environment pollution (Shrawat et al. 2008). Therefore, enhancing NUE is an ideal strategy to increase grain yield without increasing—and possibly even when decreasing—fertilizer use, decreasing investment costs, and minimizing ecological and environmental risks (Hirel et al. 2007).

NUE in cereal crops refers to the ratio of grain yield to N supplied by soil and fertilizer, which is dissected into two components: N uptake efficiency (NupE) and N utilization efficiency (NutE) (Hirel et al. 2007; Laperche et al. 2007; Moll et al. 1982; Raun and Johnson 1999). NupE is defined as the ratio of N supplied (from both natural soil levels and applied N fertilizer) to N in total shoots and biomass, and is used to describe the ability of the plant to absorb and assimilate N from the soil, which mainly occurs in vegetative roots and leaves. On the other hand, NutE is defined as the ratio of grain yield to the acquired N, which is used to indicate sink capacity to utilize N by recycling of assimilated N taking place during seed set and filling (Hirel et al. 2007). A genotype with high NUE is expected to have a high level in both NupE and NutE.

QTL (Quantitative Trait Loci) for NUE have been Mapped by Genome-Wide Markers.

A first step in understanding biological process underlying a complex trait is to discover quantitative trait loci (QTL) associated with the variation in the trait. Twenty-one QTL have previously been characterized to describe N uptake in winter wheat grown in the field (An et al. 2006). It is reported that wheat cultivars differ in their NUE (Boman et al. 1995; Cox et al. 1985; Gouis and Pluchard 1996; Van Sanford and MacKown 1987), and as many as 126 genes are predicted to be associated with N utilization and grain yield components in a spring wheat population (Habash et al. 2007; Quarrie et al. 2005). However, only a small part of the total phenotypic variation is explained by each QTL (<30%), which has limited further molecular manipulation of these mapped QTL.

SUMMARY OF THE INVENTION

An embodiment is based on the identification, in the plant genome, of genes that are associated with nitrogen utilization efficiency (NUE), and the discovery of at least one variant of the one or more genes that, when present in a plant, causes the plant to exhibit increased or elevated NUE. The increase in NUE is manifested phenotypically, for example, as increased grain yield in cereal plants. A major QTL associated with increased NUE was identified as located in chromosome 5A in hexaploid bread wheat. This QTL locus has been denominated QNue.osu-5A, and the gene of the invention is located at the QNue.osu-5A locus. Isolated and cloned forms of the gene were used to produce genetically engineered plants which validated the function of the gene. The VRN1^N gene from wheat cultivar Jagger is herein disclosed as the TaNUE1 gene (SEQ ID NO: 9).

This embodiment provides plant cultivars comprising at least one VRN1^N gene from the wheat cultivar Jagger. In some aspects, the plant cultivar is a wheat cultivar. In some aspects, the plant cultivar is not a Jagger cultivar, but may be a cross between Jagger and another cultivar. In other aspects, the plant cultivar is not a Jagger cultivar. In additional aspects, the plant cultivar further comprises plant gene

ANR1 from wheat cultivar Jagger (SEQ ID NO: 31) or from wheat cultivar 2174 (SEQ ID NO: 35).

One variation also provides methods of increasing one or more traits associated with nitrogen use efficiency (NUE) in a plant. The methods comprise the step of genetically engineering the plant to contain and express or over-express VRN1^N from wheat cultivar Jagger (SEQ ID NO: 9). In some aspects, the one or more traits associated with NUE are selected from the group consisting of heading date, chlorophyll content, grain yield, harvest index, nitrogen concentration in grain, spike number per plant, grain number per spike, biomass per plant, and a ratio of grain yield to N supplied.

Further aspects of the invention provide methods of providing a plant cultivar that exhibits increased nitrogen use efficiency (NUE). The methods comprise the steps of i) crossing a plant cultivar comprising the VRN1^N allele from wheat cultivar Jagger with a plant cultivar that does not comprise the VRN1^N allele from wheat cultivar Jagger; ii) testing F1 generation plants produced by said step of crossing for the presence of the VRN1^N allele from wheat cultivar Jagger; and iii) selecting, as a plant cultivar that exhibits increased NUE, a plant which tests positive for the presence of the VRN1^N allele from wheat cultivar Jagger.

Yet further aspects of the invention include the plant gene ANR1 from wheat cultivar Jagger (SEQ ID NO: 31) and the plant gene ANR1 from wheat cultivar 2174 (SEQ ID NO: 35). The plant gene ANR1 encodes a protein that interacts physically with the protein encoded by VRN1^N. Plant cultivars comprising at least one plant gene ANR1 from wheat cultivar Jagger and/or from wheat cultivar 2174 are also compassed. In some aspects, the plant cultivar is a wheat cultivar. In other aspects, plant cultivar is not a Jagger cultivar or is not a 2174 cultivar. In additional aspects, the plant cultivar further comprises plant gene VRN1^N from wheat cultivar Jagger. Methods of making such cultivars, either by genetic modification or by selective breeding, are also encompassed.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**: QNue.osu-5A. A major QTL responsible for multiple phenotypic traits that vary in response to variations in N amounts was mapped by testing in Jagger×2174 population. Plants were grown in N-deficient soil with normal levels of other essential nutrients. The N-stressed plants were then supplied with 100-mg N/pot (A) and 25-mg N/pot (B).

FIG. **2**: Candidate genes for TaNUE1 on QNue.osu-5A according to genomic sequences of collinear region in rice. Genes that are mapped between Gene1 and CDO708 are candidate genes for TaNUE1.

FIG. **3**A and FIG. **3**B: FIG. **3**A: Sequence of *Triticum aestivum* gene Gene 1 from A, Jagger cultivar (SEQ ID NO: 1) and FIG. **3**B: 2174 cultivar (SEQ ID NO: 2).

FIG. **4**A and FIG. **4**B: FIG. **4**A: Sequence of *T. aestivum* gene PCS from A, Jagger cultivar (SEQ ID NO: 3) and FIG. **4**B: 2174 cultivar (SEQ ID NO: 4).

FIG. **5**A and FIG. **5**B: FIG. **5**A: Sequence of *T. aestivum* gene CYB5 from A, Jagger cultivar (SEQ ID NO: 5) and FIG. **5**B: 2174 cultivar (SEQ ID NO: 6).

FIG. **6**A and FIG. **6**B: FIG. **6**A: Sequence of *T. aestivum* gene AGLG1 from A, Jagger cultivar (SEQ ID NO: 7) and FIG. **6**B: 2174 cultivar (SEQ ID NO: 8).

FIG. **7**A and FIG. **7**B: FIG. **7**A: Sequence of *T. aestivum* gene VRN1 from A, Jagger cultivar (SEQ ID NO: 9) and FIG. **7**B: 2174 cultivar (SEQ ID NO: 10).

FIG. **8**A and FIG. **8**B: FIG. **8**A: Sequence of *T. aestivum* gene CYS from A, Jagger cultivar (SEQ ID NO: 11) and FIG. **8**B: 2174 cultivar (SEQ ID NO: 12).

FIG. **9**A and FIG. **9**B: FIG. **9**A: Sequence of *T. aestivum* gene PHY from A, Jagger cultivar (SEQ ID NO: 13) and FIG. **9**B: 2174 cultivar (SEQ ID NO: 14).

FIG. **10**A and FIG. **10**B: FIG. **10**A: Sequence of *T. aestivum* gene GT1 from A, Jagger cultivar (SEQ ID NO: 15) and FIG. **10**B: 2174 cultivar (SEQ ID NO: 16).

FIG. **11**A and FIG. **11**B: FIG. **11**A: Sequence of *T. aestivum* gene STR from A, Jagger cultivar (SEQ ID NO: 17) and FIG. **11**B: 2174 cultivar (SEQ ID NO: 18).

FIG. **12**A and FIG. **12**B: FIG. **12**A: Sequence of *T. aestivum* gene KIN from A, Jagger cultivar (SEQ ID NO: 19) and FIG. **12**B: 2174 cultivar (SEQ ID NO: 20).

FIG. **13**A and FIG. **13**B: FIG. **13**A: Sequence of *T. aestivum* gene CBP1b from A, Jagger cultivar (SEQ ID NO: 21) and FIG. **13**B: 2174 cultivar (SEQ ID NO: 22).

FIG. **14**A and FIG. **14**B: FIG. **14**A: Sequence of *T. aestivum* gene USP from A, Jagger cultivar (SEQ ID NO: 23) and FIG. **14**B: 2174 cultivar (SEQ ID NO: 24).

FIG. **15**A and FIG. **15**B: FIG. **15**A: Sequence of *T. aestivum* gene EX from A, Jagger cultivar (SEQ ID NO: 25) and FIG. **15**B: 2174 cultivar (SEQ ID NO: 26).

FIG. **16**A and FIG. **16**B: FIG. **16**A: Sequence of *T. aestivum* gene CDO708 from A, Jagger cultivar (SEQ ID NO: 27) and FIG. **16**B: 2174 cultivar (SEQ ID NO: 28).

FIG. **17**: Recombinant lines that were tested for genetic effects of QNue.osu-5A on heading date in N-deficient soil. Results are shown in tabular form. Three critical recombinant lines, D1032, P55 and D695, indicate that TaNUE1 is in the targeted gene between PCS1 and CYS1.

FIG. **18**A and FIG. **18**B: Genetic and physical maps of TaNUE1. FIG. **18**A: Genetic map of the location of the indicated traits.

FIG. **18**B: Final physical map of TaNUE1. TaNUE1 was located between two flanking markers PCS1 and CYS1, in the region where only three candidate genes, CYB5, AGLG1, and VRN1, were present.

FIG. **19**A-FIG. **19**F: Genetic effects of VRN1 in seven critical recombinant lines tested in the field. The experiments were conducted at OSU Perkins Research Station. FIG. **19**A: spikes per plant; FIG. **19**B: grains per spike; FIG. **19**C: weight (g) per 1000 grains; FIG. **19**D: grain yield; FIG. **19**E: biomass; FIG. **19**F: harvest index.

FIG. **20**A and FIG. **20**B: In vitro protein interactions of ANR1 with VRN1 and AGLG1. FIG. **20**A: ANR1 and VRN1 proteins and FIG. **20**B: ANR1 and AGLG1 proteins. ANR1, VRN1a, AGLG1a were from Jagger, whereas VRN1b and AGLG1b were from 2174. M: protein molecular weight markers.

FIG. **21**A-FIG. **21**F: In vivo protein interactions between ANR1 and VRN1. FIG. **21**A: The subcellular location of TaANR1-YFP protein expressed by pEG101 in the nucleus (N) of living cells in tobacco leaves. FIG. **21**B: TaANR1-YFP-pEG101 cell nucleus was stained with 4', 6-diamidino-2-phenylindole (DAPI). FIG. **21**C: VRN1-pEG201-YN and ANR1-pEG202-YC proteins were expressed in the nucleus (N) of living cells. FIG. **21**D: The interacting proteins were stained with DAPI. FIG. **21**E: The image (A) was taken with a bright filter (BF) to indicate the background of the leaves. FIG. **21**F. The overlay images align the location of YFP with the DAPI-stained nucleus.

FIG. **22**A-FIG. **22**D: Regulation of VRN1^N in normal wheat and transgenic wheat plants. FIG. **22**A: Regulation of VRN-A1^N transcripts by N in normal wheat grown in different soils. FIG. **22**B: Regulation of heading date by N in normal wheat grown in different soils. FIG. **22**C: Regulation of VRN-A1^N transcripts by RNAi in transgenic wheat grown in yellow soil. FIG. **22**D: Regulation of heading date by RNAi in transgenic wheat grown in yellow soil.

FIG. **23**A-FIG. **23**E: ANR1 natural mutant and transgenic plant. FIG. **23**A: Variation of ANR1 transcripts between Jagger and 2174. FIG. **23**B: A PCR marker for ANR1 between the Jagger and 2174 alleles. For FIG. **23**A and FIG. **23**B: lanes 1 and 2 are independent samples from Jagger; lanes 3 and 4 are two independent samples from 2174; and M=molecular weight markers. FIG. **23**C: A diagram of indel locations and sequences in ANR1 between the Jagger and 2174 alleles. FIG. **23**D: Regulation of ANR1 transcripts by N and RNAi in transgenic wheat. FIG. **23**E: Comparison of typical transgenic plant carrying ANR1::RNAi and a non-transgenic plant.

FIG. **24**: Amino acid sequence of the VRN1 protein from the Jaggar cultivar (SEQ ID NO: 29).

FIG. **25**A-FIG. **25**D: FIG. **25**A: amino acid sequence of ANR1 protein (SEQ ID NO: 30) from Jagger; FIG. **25**B: nucleotide sequence of ANR1 gene (SEQ ID NO: 31) from Jagger; FIG. **25**C: amino acid sequence of ANR1 protein (SEQ ID NO: 34) from 2174; and FIG. **25**D: nucleotide sequence of ANR1 gene (SEQ ID NO: 35) from 2174.

FIG. **26**A and FIG. **26**B: FIG. **26**A: amino acid sequence of HOX1 gene protein (SEQ ID NO: 32) from Jagger; and FIG. **26**B: nucleotide sequence of HOX1 gene (SEQ ID NO: 33) from Jagger.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Wheat genetics experiments have allowed the identification of a major QTL QNue.osu-5A associated with high NUE in plants in a population of recombinant inbred lines generated from two winter wheat cultivars, Jagger and 2174. The genes included within the QTL are located on wheat chromosome 5A at locus QNue.osu-5A, in the genomic region between the two flanking genes GENE1 and CDO708 (see FIG. **2**). 44 genes (encoding proteins) in the collinear region in rice, were analyzed, including: 1) OSJNBa0069E14.12 (hypothetical protein), 2) OSJNBa0069E14.13 (dehydrogenase), 3) OSJNBa0069E14.3 (growth inhibitory protein ING1), 4) OSJNBa0069E14.14 (antifreeze glycoprotein precursor), 5) SRPK4 (Serine/Threonine rich protein kinase), 6) OSJNBa0069E14.15 (reductase), 7) OSJNBa0069E14.10 (unknown protein), 8) OSJNBa0069E14.4 (hydrogenase), 9) OSJNBa0069E14.16 (helicase), 10) OSJNBa0069E14.5 (arginine-rich protein), 11) OSJNBa0069E14.17 (ammonium transporter), 12) OSJNBa0069E14.6 (beta-D-glucan exohydrolase), 13) OSJNBa0069E14.7 (exoglucanase precursor), 14) OSJNBa0069E14.20 (hypothetical protein), 15) OSJNBa0069E14.21 (circumsporozoite protein-like protein), 16) OSJNBa0069E14.22 (hypothetical protein), 17) OSJNBa0069E14.8 (EX, exohydrolase), 18) OSJNBa0069E14.24 (hypothetical protein), 19) OSJNBa0069E14.23 (tousled-like protein kinase), 20) OSJNBa0047E24.24 (expressed protein), 21) OSJNBa0047E24.26 (USP, expressed protein), 22) OSJNBa0047E24.27 (CBP, putative stress-related protein), 23) OSJNBa0047E24.25 (KIN, kinesin-like protein), 24) OSJNBa0047E24.22 (STR, strictosidine synthase), 25) OSJNBa0047E24.21 (transcriptional adaptor), 26) OSJNBa0047E24.20 (hypothetical protein), 27) OSJNBa0047E24.19 (expressed protein), 28) OSJNBa0047E24.18 (expressed protein), 29) OSJNBa0047E24.17 (GT: glutathione transporter, oligopeptide transporter protein), 30) OSJNBa0047E24.15 (hypothetical protein), 31) OSJNBa0047E24.14 (transposase) (wheat orthologue, if present), 32) OSJNBa0047E24.13 (ribosomal protein L6), 33) OSJNBa0047E24.10 (hypothetical protein), 34) OSJNBa0047E24.9 (phytochrome C), 35) OSJNBa0047E24.8 (DNA topoisomerase), 36) OSJNBa0047E24.7 (potassium channel protein), 37) OSJNBa0047E24.5 (cysteine protease), 38) OSJNBa0047E24.2 (VRN-A1, AP1-like MADS box protein), 39) OSJNBa0047E24.1 (AGLG1, MADS-box transcriptional factor), 40) EAY91897 (CYB5, Cytochrome b5-like), 40) 3615.7 (AAM22488.1, putative phytochelatin synthetase), 40) 3615.5 (AAG45493.1, DUF1618), 42) 3615.4 (ABC transporter), 43) 3615.3 (serine/threonine kinase), 44) 3615.2 (cleavage stimulation factor subunit 1). 45) 3615.1 (putative mitochondrial carrier protein).

In particular, the following genes were identified as associated with increased NUE: CYB5; AGLG1 (OSJNBa0047E24.1); VRN1 (OSJNBa0047E24.2) by experiments on critical RILs that have crossovers at QNue.osu-5A, as shown FIG. **17**.

More particularly, the VRN1 gene from Jagger cultivar (SEQ ID NO: 9) has been identified as a TaNUE1 responsible for NUE in plants. VRN1 is hereafter referred to as VRN1^N for its reaction to N.

Generally, the invention encompasses the VRN1^N gene from Jagger cultivar (SEQ ID NO: 9) which encodes the VRN1 protein (FIG. **24**, SEQ ID NO: 29), as well as sequences which encode proteins or polypeptides that are at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or even more (e.g. 96, 97, 98, 99 or 100%) identical or similar to VRN1. By "identical" or "identity" we mean that the primary sequence of amino acids in the protein/polypeptide is the same when the sequences are aligned (excluding regions where deletions or insertions have occurred). By "similar" or "similarity" we mean that the primary sequence of amino acids in the protein/polypeptides, when rice and wheat translation products are aligned, is either identical (the amino acids at corresponding positions are the same) or are contains only conservative substitutions, e.g. the amino acids at both positions is negatively charged, positively charged, aliphatic, etc. Those of skill in the art are familiar with methods for determining levels of identity and similarity (e.g. by using software programs that are designed to provide this information) and are also familiar with interpreting the results and significance of such analyses. As is the case for determining identity, regions of insertions or deletions may be excluded from such analyses, or may be "weighted" so as to taken into account in a final analysis, or more than one value for identity or similarity may be provided, e.g. a value may be provided only for regions where no insertions or deletions have taken place. Further, those of skill in the art will recognize that the genes encoding the proteins/polypeptides may or may not have high levels of identical sequences when compared to one another, due to the redundancy of the genetic code (i.e. several different codons may encode the same amino acid). Thus, the level of identity (which may also be referred to as "homology") between the gene sequence of the VRN1^N gene may be the same as described above for the proteins/polypeptides, but may also be lower, e.g. 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% or more, and so on, as described above.

VRN1^N or variants thereof cause increased NUE in plants which contain and express VRN1^N and/or its variants, resulting in advantageous traits such as early heading and increased grain yield in cereal crops, when compared to plants containing only wild type genes.

Generally, the present invention encompasses NUE-associated nucleic acid sequences (which may be genes), methods for their use, and plants which contain the sequences, the plants having been produced either by cross-breeding or by genetic engineering. By "NUE-associated nucleic acid sequences" we mean sequences which have been identified as impacting (influencing, governing, controlling, responsible for, etc.) the efficiency of nitrogen utilization by a plant, e.g. VRN1^N from cultivar Jaggar. The sequences may be associated with one or both of N uptake efficiency (NupE) and N utilization efficiency (NutE), or with other factors which have an impact on N utilization by the plant.

In some embodiments, the NUE-associated nucleic acid sequence is a gene which encodes a protein. Generally, the protein is involved in nitrogen uptake and sequestration in the plant, or with utilization of nitrogen that has been taken up, or both. The nucleic acid sequences for VRN1^N are presented in FIG. **7**A and FIG. **7**B. For convenience, a NUE-associated gene may be referred to herein and in the Examples section below as "TaNUE1", i.e. the gene has been named (or renamed) to accord to its newly-recognized functions and capabilities. A series of such genes may be referred to as TaNUE1-1, TaNUE1-2, etc. In some aspects, TaNUE1 is the VRN1^N gene from the Jaggar cultivar.

Generally, the enhanced or increased NUE caused by a TaNUE1 of the invention is at a level that is at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100% or even higher than the level of NUE that is displayed by a control plant (e.g. a wild type plant, or a reference plant that has not been genetically engineered to contain and express or overexpress the variant), or even 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold or more higher. Such increases are determined by measuring at least one detectable parameter, e.g. an objective criteria or trait associated with increased with increased NUE. Examples of such criteria or traits include but are not limited to: heading date; chlorophyll content of plant, e.g. in the leaves; angler degree of leaves; tillers per plant; spikes per plant; biomass; harvest index; grains per spike, grain weight, grain yield, content of nitrogen and other nutrients in grains and plant tissues, etc.

One embodiment also provides genetically engineered plants that have been genetically modified, using molecular biology techniques, to contain and express at least one VRN1^N gene (e.g. from Jagger) and/or at least one ANR1 gene (e.g. from Jagger or 2174), or variants thereof as described herein. In other words, plants comprising multiple copies of the genes described herein are also encompassed. For example, the plant may comprise a "native" gene and one or more copies of the same gene, or a function conservative variant thereof, or one or more copies of a different gene (or genes), that have been introduced by genetic engineering or selective breeding. A function conservative variant has the same or substantially the same level of an activity of interest (e.g. increasing NUE) as the parent molecule, e.g. at least about 50, 60. 70. 80 or 90% or more, of the activity of the parent molecule.

The genetically engineered plants of the invention are transformed using any of the many methods that are known in the art. Exemplary methods include but are not limited to: particle bombardment using small metal particles, e.g. gold or tungsten, coated with DNA and which are shot into young plant cells or plant embryos; electroporation, whereby transient holes are made in plant cell membranes using an electric shock, thereby allowing DNA to enter, etc.

One variation of the invention also encompasses nucleic acid sequences that are not identical to those provided herein, but which are at least about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% homologous to those sequences. The sequences may be the result of point mutations and may or may not change the encoded amino acid. Other variations of the sequences include those which result from various deletions or insertions, so long as the resulting encoded amino acid sequence has substantially the same activity with respect to plant NUE as the amino acid sequence encoded by the nucleotide sequences disclosed herein. Generally, the activity level is at least about 50, 60, 70, 80, or 90% or even greater, than that of the original encoded amino acid sequence, and may even be greater than that of the original, parent sequence. Further possible changes include but are not limited to: the insertion or removal of restriction enzyme cleavage sites, incorporation of sequences which assist in manipulation of the sequence or the amino acid sequence encoded thereby (e.g. the inclusion of sequences encoding a Histidine tag, or sequences which function as a label of the nucleotides); etc. Such nucleic acid sequences may be single or double stranded. In addition, homologous or base-paired sequences such as cDNA, mRNA, DNA-RNA hybrids, etc. that correspond to or are based on the sequences disclosed herein are also encompassed.

The amino acid sequences of an embodiment may also vary somewhat from those that are encoded by the nucleotide sequences disclosed herein. For example, various conserved amino acid substitutions may be present, as may certain deletions (typically at the amino or carboxy termini), or even non-conserved amino acid substitutions may occur, so long as the changes do not significantly attenuate the NUE activity of the amino acid sequence. The variations may be due to, for example, natural variations in sequence among different species or cultivars, the addition of a leader sequence to promote secretion, the addition of a sequence to promote translocation of the sequence within the cell, the addition of tagging sequences which facilitate tracking or isolation of polypeptides, the addition or elimination of glycosylation sites, sequences which improve or decrease solubility of a polypeptide, etc. Generally, the altered sequences will exhibit identity (similarity) to the sequences disclosed herein of at least about 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or higher. Such variations can be tolerated and are encompassed by the present invention so long as the resulting sequence displays or retains at least about 75%, preferably 80, 85, 90%, or at least about 95% or more of the activity of the sequences disclosed herein. In some cases, such changes may cause an increase in activity. All such variations of the sequences disclosed herein are encompassed by the present invention.

In other embodiments of the invention, plants containing and expressing the NUE-associated VRN1^N are produced by purposeful, directed plant breeding techniques, and are not necessarily genetically engineered. Those of skill in the art are familiar with methods used to select, cross and cultivate suitable plants, and to identify plant progeny of interest which display a desired trait, such as a trait that is indicative of increased NUE. Further, the presence of one or more nucleic acid sequences of the invention in such progeny plants can be confirmed by known methods of gene sequencing, or identification and characterization of mRNA or an amino acid sequence that is encoded by the gene.

The invention also encompasses transgenic (genetically modified) plants which contain and express or overexpress VRN1^N, as well as method of making such plants. Exemplary plants that can be genetically modified as described herein include but are not limited to: grasses, e.g. members of the monocot families Poaceae or Gramineae which may also be known as cereals, grains or cereal grains, examples of which include but are not limited to wheat, rice, maize (corn), triticale, oats, barley, rye, spelt, sorghum, millet, fonio, and others; members of the Polygonacea family such as buckwheat; members of the Amaranthaceae family such as quinoa and various amaranths. In addition, one of skill in the art will recognize that the genetically engineered plants of the invention may also include: vegetable plants (e.g. carrots, tomatoes, onions, squash, beets, lettuce, peppers, cabbage, potatoes, etc.); various legumes or beans such as peas, soybeans, peanuts, etc.; herbs; various ornamental plants; plants which produce berries; plants which produce materials for use in various manufactures such as cotton, flax, etc.; various species of trees and shrubs; plants or other organisms which are used to generate biofuel (e.g. switch-grass, *Brachypodium distachyon*, hemp, sunflowers, soy, rapeseed, photosynthetic algae, etc.). Any plant or organism which utilizes nitrogen may benefit from being genetically engineered to contain and express the NUE-associated nucleic acid sequences described herein.

Progeny of the genetically engineered and selectively bred plants described herein are also encompassed, as are all parts or portions of the plants, e.g. seeds stalks, leaves, roots, etc., and all stages of the life cycle of the plant, e.g. embryos, cuttings, grafts, etc.

Experimental evidence provided herein (see the Examples below) demonstrates that $VRN1^N$ is TaNUE1 at QNue.osu-5A in bread wheat. In addition, direct interaction of the $VRN1^N$ protein with ANR1, and regulation of $VRN1^N$ and ANR1 by N in normal and transgenic wheat plants, further suggests that the gene ANR1 may also be involved in NUE. Thus, further aspects of the invention include transgenic plants and methods of making the plants which include one or more copies of ANR1, optionally with $VRN1^N$ in the same plant. Further experiments described below showed that the protein encoded by the HOX1 gene, HOX1, is also involved in plant development (e.g. due to its interaction with $VRN1^N$). Thus, further aspects of the invention include transgenic plants and methods of making the plants which include one or more copies of HOX1, optionally with $VRN1^N$ and/or ANR1 in the same plant. For example, in winter wheat, the VRN1-HOX1 interaction has a significantly stronger effect on e.g. flowering time than the VRN1-ANR1 interaction.

In some aspects, the genes described herein are used as molecular markers, e.g. for gene pyramiding to produce novel wheat cultivars with desirable traits, such as high NUE. Gene pyramiding is a method aimed at assembling multiple desirable genes (markers) from multiple parents into a single genotype. This technique can be applied to enhance NUE, for example, using two or more of the genes described herein, e.g. $VRN1^N$ and/or ANR1 (e.g. from cultivars such as Jagger and 2174, and variants thereof) by selecting for two genes at a time. Selection can be performed, e.g. by designing and using oligonucleotide primers specific for the genes described herein (e.g. $VRN1^N$, ANR1, etc.), and such primers are also encompassed by the invention. The design of primers to amplify a sequence of interest is known in the art, e.g. primers with sequences that are base pair with a portion of a sequence of interest. One advantage of using markers is that this allows selection of additional QTL-allele-linked markers that have the same phenotypic effect. Once identified, several marker genes can be incorporated into a plant, e.g. by genetic engineering or by selective breeding, in order to promote a particular desirable phenotype, e.g. highly efficient use of nitrogen.

The following Examples serve to illustrate various embodiments of the invention but should not be construed so as to limit the invention in any way.

EXAMPLES

Example 1. Discovery of a Major QTL for NUE

Construction of a Genetic Map for Winter Wheat

A total of 365 markers were mapped in the Jagger×2174 population of 96 recombinant inbred lines (RILs) generated from a cross between two locally adapted winter wheat cultivars Jagger and 2174. This high density of genetic map has been used successfully to locate QTLs for complex traits related to developmental process for stem elongation and winter dormancy release (Chen et al. 2009), heading date and physiological maturity (Chen et al. 2010), resistance to powdery mildew (Chen et al. 2009), resistance to leaf rust (Cao et al. 2010), resistance to stripe rust (Fang et al. 2011). This genetic map has now been used to locate a major QTL for NUE in this study.

Discovery of a Major QTL for NUE

Three sets of populations of 96 recombinant inbred lines (RILs) and their parental lines were tested for segregation for responses to nitrogen (N). The experiments were performed in pots in a greenhouse, where conditions were controlled for temperature, photoperiod, and moisture conditions in order to reduce interactions between genetic and environmental factors on N utilization.

The first set population was grown in a commercial growth media, and only the heading date was recorded for the purpose of comparison with another two sets of populations that were tested for the responses to N fertilizer. The second and third sets of population plants were first grown in soil with N-deficiency but with an adequate supply of other nutrients. The initial plant available nutrient levels of the soil were, nitrate N (2.4 $mgKg^{-1}$), P (42.2 $mgKg^{-1}$), K (115.5 $mgKg^{-1}$), SO_4 (6.4 $mgKg^{-1}$), Ca (420.7 $mgKg^{-1}$), Mg (81.9 $mgKg^{-1}$), Fe (28.7 $mgKg^{-1}$), Zn (0.9 $mgKg^{-1}$), B (0.14 $mgKg^{-1}$), Cu (0.3 $mgKg^{-1}$), and organic matter content (OM: 0.69%). The soil had a low organic matter content (0.39%) and moderate pH value (5.83).

The parental lines and second and third sets of populations showed no significant difference in morphological trait at young seedlings when grown in N-deficient soil, indicating that these two cultivars have similar tolerance to N stress. After they were fertilized with 100 mg N/pot (=54.06 mg N/kg soil, 100N) and 25 mg N/pot (=13.51 mg N/kg soil, 25N) respectively, these population plants showed significant segregation in agronomic and physiological traits.

Eleven traits were characterized for two populations supplied with different N levels of soils. When the phenotypic traits were analyzed with the genetic map, it was found that a major QTL was associated with variation in all of the traits studied (FIG. 1). This major QTL locus was located in chromosome 5A, where the vernalization gene $VRN1^N$ resides. Hence, this QTL locus was designated QNue.osu-5A.

Genetic effects of QNue.osu-5A on each of the traits are summarized in Table 1. Overall, the following conclusion can be made: 1) QNue.osu-5A was associated with strong responses to N fertilizers at both N levels supplied to the soil; 2) most of the phenotypes characterized in the preliminary experiments showed larger segregation in the population treated with 100N than 25N; 3) fertilizer N level variation resulted in various effects on different phenotypes characterized in this study.

Heading date is a most sensitive trait to N fertilizer. At the 100N fertilizer level, QNue.osu-5A explained as much as 68.2% of the total phenotypic variation, and at the 25N fertilizer level, it explained 51% of the total phenotypic variation. In the commercial growth medium, it accounted for 20.6% of the total phenotypic variation (data not shown).

Chlorophyll content of the leaf is a trait that is directly affected by N level. 20.7% of the total phenotypic variation in 100N population could be explained by QNue.osu-5A, but no significant genetic effect in 25N population was detected at this QTL.

Grain yield is the most important trait for utilization of N fertilizers. Grain yield of this experiment had a typical response to N fertilization. Plant grain yield of the 100N population was 0.601 g/plant, increased 121% in comparison to 0.272 g/plant for the 25N population. Significantly, about 55.3% and 38.5% of the total variation in grain yield in 100N and 25N populations were respectively explained by QNue.osu-5A.

The N content of wheat grains also showed a direct link to the QTL at QNue.osu-5A, which had a LOD score value of 3.3 and 1.9 explaining 15.4% and 8.8% to the total phenotypic variation in 25N and 100N populations, respectively.

It is noteworthy that these data were obtained from the population plants grown under controlled temperature and light conditions through the life cycle. Moreover, these plants are a winter type but they were not vernalized at all, because the two parental lines had different vernalization requirements. The major aim of this experiment was to find a major QTL for NUE under controlled conditions, from which a starting point could be opened to enter the NUE gene network for further studies on how the complex trait is regulated under varying environments.

TABLE 1

Genetic effects of ONue.osu-5A on 11 traits related to N utilization and yield
Analysis of sequences of collinear region of rice genome

	100N		25N	
Traits	LOD	R2 (%)	LOD	R2 (%)
Heading date	22.8	68.2	14.6	51.0
Chlorophyll % in leaf	4.2	19.4	NS	NS
Angler degree of 2nd leaf	1.9	8.8	NS	NS
Tillers per plant	5.8	25.4	3.1	13.9
Spikes per plant	4.3	18.6	4.8	22.7
Grains per spike	13.5	47.4	9.1	36.4
Grain weight	3.5	15.9	NS	NS
Grain yield	16.5	55.3	10.2	38.5
Biomass	1.4	6.4	2.6	13.2
Harvest index	29.1	74.9	19.4	60.9
N% in grains	1.8	8.8	3.3	15.4

Sequences of regions collinear to QNue.osu-5A in rice (GenBank accession number AP008209) were analyzed. QNue.osu-5A is located in the region encompassing the VRN1 locus and is conserved among diploid wheat *T. monococcum*, rice and other cereal crops (Yan et al. 2003). Several genes have been successfully mapped in genome A of bread wheat (FIG. **1** and FIG. **2**).

The gene responsible for QNue.osu-5A is designated TaNUE1, the first gene for NUE in *Triticum aestivum*. Cloning and characterization of TaNUE1 will be an entry point for construction of the gene network for NUE in wheat.

Example 2. Narrowing Down the Genomic Region Encompassing TaNUE1

As described above. TaNUE1 at the QTL locus QNue.osu-5A on wheat chromosome 5A was previously identified as one among 44 orthologous genes (encoding proteins) in the 344-kb collinear region on chromosome 3 in rice. To further elucidate the identity of TaNUE1, RIL23 carrying the Jagger QNue.osu-5A allele was backcrossed with the parental line 2174 and a total of 6,410 BC_1F_3 plants derived from BC_1F_2 plants heterozygous at QNue.osu-5A were generated. PCR markers for GENE1 and CDO708 that flanked the gene responsible for QNue.osu-5A (original FIG. **2**) were used to genotype the 6,410 individual plants and 106 crossovers were found between GENE1 and CDO708. Progeny plants of seven critical recombinant plants were tested for their reactions to N.

Based on progeny tests of 15 recombinant lines (FIG. **17**), TaNUE1 was delimited between GENE1 and CDO708.

Heading date is one of several phenotypes associated with nitrogen use efficiency in winter wheat. Progeny plants generated from 15 of the 106 recombinant $BC_1F_{2:3}$ lines were tested for the segregation of heading date, and crossovers in these plants were distributed along the targeted region (nor shown). As the original RILs were tested to map QNue.osu-5A, the progeny plants were grown in the same type of N-deficient soil, fertilized with 100 mg N/pot (=54.06 mg N/kg soil, 100N) 12 weeks after planting, and not vernalized. The integration of phenotypes and genotypes of these recombinant lines showed that the gene for the segregation of heading date was located in the region between two gene markers for PCS1 and CYS1 (shown in tabular form in FIG. **18**). Those plants carrying the Jagger allele (158.3 days) headed up significantly earlier than those plants carrying the 2174 allele (174 days). The averaged difference between the two alleles in the 15 recombinant lines was similar to the difference between the two parental lines (16 days). The Jagger allele for early heading showed a dominant effect over the 2174 allele for late heading in the heterozygous $BC_1F_{2:3}$ population, and the acceleration of heading date by the Jagger allele was confirmed in three BC_1F_3 populations (FIG. **17**).

When the seven critical recombinant plants were grown in commercial soils with sufficient N and vernalized with 3 weeks, the Jagger allele for early heading was dominant over the 2174 allele for late heading, and the average difference between the two alleles was 25 days. Further comparison of the heading date in the N experiments and the three week vernalization experiments showed that the segregation pattern in heading date was similar in each of the populations (Table 2). These results suggested that the genes for N and low temperatures were located in the same region, where only three genes were encompassed including CYB5, AGLG1 and $VRN1^N$.

TABLE 2

Comparison of the effect of QNue.osu-5A on flowering time in different soils

Plant ID	Yellow soil A	Yellow soil B	Commercial soil H	A	B	H
D1032	182	203	194	148	147	149
P55	159	193	—	93	122	—
D695	174	203	193	92	139	98
D731	178	179	175	133	141	142
D1061	159	163	157	90	94	94
L447	168	206	—	86	147	—
T657	143	201	—	89	159	
Jagger	155			84		
2174		177			122	

Phenotypic Effects of TaNUE1 in the Field

Seven critical recombinant lines, each having a crossover at QNue.osu-5A, were tested in the field for effects of TaNUE1 on productivity. The experiments were performed at OSU Perkins Research Station near Stillwater for two years, in a field where no N fertilizer had been used for two consecutive seasons. Forage was grown in the field to level soil fertility for all lines tested. Plots were arranged in a completely randomized design with three replications for the recombinant lines and parents.

When the seven critical recombinant lines were tested and the basal fertility in the soil was 15 lbs. per acre for NO_3^-—N, spike number per plant (FIG. **19**A), grain number per spike (FIG. **19**B), and weight per thousand grains (FIG. **19**C) all were relatively increased. As a result, grain yield was increased by 18.1% (FIG. **19**D). The significant increase of grain yield was due to increases of both biomass (12.7%, FIG. **19**E) and harvest index (4%, FIG. **19**F). These results indicated that the N resources available in the soil were more efficiently utilized throughout the whole life cycle in those lines carrying the Jagger allele than those lines carrying the 2174 allele at QNue.osu-5A.

When the seven critical recombinant lines were further tested and the basal fertility in the soil was decreased to 10.3 lbs. per acre for NO_3^-—N, plant productivity was dramatically decreased, and no significant difference was observed between the two alleles in any of the grain yield components or in grain or biomass productivity (FIG. **19**A-F). The observation was consistent with the previous results that the LOD value of QNue.osu-5A was significantly decreased when RILs having diverse genetic backgrounds were tested in 25 mg N/pot compared with 100 mg N/pot. These results confirmed that the TaNUE1 is a gene within the targeted region between the two gene markers, PCS1 and CYS1. Three candidate genes were included in this region CYB5, AGLG1 or $VRN1^N$.

Example 3 Identification of Candidate Genes for TaNUE1

Allelic Variation in Candidate Genes for TaNUE1

Only three genes, CYB5, AGLG1, and $VRN1^N$, were identified as candidate genes for TaNUE1. A comparison of allelic variation in these three candidates showed no difference in the gene region from the start codon to the stop codon of CYB5, but a SNP resided in its downstream region at the 3' end, permitting development of a PCR marker for mapping. There was also one SNP in the AGLG1 gene region which resulted in a point mutation in the AGLG1 protein: serine (Ser) in Jagger and alanine (Ala) in 2174. There were two SNPs in $VRN1^N$ which resulted in two point

mutations in the VRN1 protein. One SNP occurred in exon 4, producing a leucine (Leu) at position 117 in the VRN1a protein encoded by the Jagger allele but a phenylalanine (Phe) at the same position in VRN1b encoded by the 2174 allele. This Leu^{117}/Phe^{117} substitution occurred within the conserved K-box which is located at positions from 89 to 174. The second SNP occurred in exon 7, producing an alanine (Ala) at position 180 in VRN1a but a valine (Val) at the same position in VRN1b, and the Ala^{180}/Val^{118} substitution occurred in the divergent C-terminus of the protein.

No gene related to NUE has previously been found or cloned in wheat or any other crop. AtANR1, a NO_3^--inducible *Arabidopsis* gene, is a MADS-box gene and plays a key role in regulating lateral root growth in response to changes in the external NO_3^- supply in *Arabidopsis* (Zhang and Forde 1998). The plant MADS-box proteins may form protein complexes, in which one MADS-box protein may positively or negatively regulate the expression of another MADS-box gene in a direct interaction manner (Riechmann and Meyerowitz 1997; Jack 2004). In *Arabidopsis*, another several MADS-box genes, e.g. AGL14, AGL16, AGL19, SOC1 and AGL21, have been reported to respond to N fertilizers (Gan et al. 2005). Both VRN-A1 and AGLG1 belong to the MADS-box gene family. Based on genetic association, allelic variation and predicted protein function, both AGLG1 and VRN1 were viable candidates for TaNUE1. Therefore, further properties of these proteins were investigated.

A Direct Interaction of VRN1 Protein with ANR1

In order to test if there is cross-talk (interaction) between the wheat orthologous protein of AtANR1 and $VRN1^N$ or AGLG1, specific primers were designed to amplify cDNA of ANR1 from Jagger, and ANR1, $VRN1^N$ and AGLG1 proteins were expressed in *E. coli*. ANR1 and VRN1 proteins showed strong interactions in vitro (FIG. **20**A), but no interaction was observed between ANR1 and AGLG1 proteins (FIG. **20**B). The in vitro interaction result suggested than $VRN1^N$ rather than AGLG1 was TaNUE1. ANR1 was cloned using the pEG101-YFP vector and the construct was transformed into tobacco leaves. As shown in FIG. **21**A-FIG. **21**B, enriched yellow fluorescent signals of ANR1-yellow fluorescent protein (YFP) were detected predominantly in the nucleus, which was the same pattern observed for VRN1 (Li et al., 2013), suggesting that $VRN1^N$ and ANR1 may have in vivo interaction in plants. Next, $VRN1^N$ was cloned into the pEG201-YN vector and ANR1 was cloned into the pEG202-YC vector, and in vivo protein interactions were analyzed by bimolecular fluorescence complementation (BiFC). When $VRN1^N$-YN and ANR1-YC were simultaneously expressed in the same cell, yellow fluorescence was observed in the nucleus (FIG. **21**C-FIG. **21**F). The results confirmed that $VRN1^N$ and ANR1 proteins exhibit direct binding in plants, and thus they may function in the same N metabolism pathway.

Example 4. Regulation of $VRN1^N$ Transcripts by N in Normal Wheat and Transgenic Wheat Plants

RT-PCR was used to test whether the transcripts of $VRN1^N$ were regulated by nitrogen. The parental Jagger and three RILs carrying the Jagger $VRN1^N$ allele were tested in the same type of yellow soil that was used to discover QNue.osu-5A. Commercial soil was used as a control. In both of the soils tested, the $VRN1^N$ transcripts in fertilized plants were lower than in non-fertilized plants, indicating the $VRN1^N$ transcripts were down-regulated by N (FIG. **22**A). The higher $VRN1^N$ transcriptional level was associated with earlier heading, and the heading date of the fertilized plants was delayed (FIG. **22**B).

RNAi was used to interfere with expression of VRN1^N in Jagger as a host plant. Two individual transgenic plants were successfully generated. T_1 populations were tested in yellow soil (as above). VRN1^N transcript levels were dramatically reduced in positive plants compared with non-transgenic plants, and fertilization of the positive plants with N decreased VRN1^N transcript levels even further, in comparison to non-fertilized positive plants. (FIG. **22**C). The heading date of non-transgenic plants was 130 days, which was delayed to 138 days in the positive transgenic plants, and to 143.4 days in positive transgenic plants fertilized with N (FIG. **22**D). These results provided direct evidence that VRN1^N functioned in the N metabolism and flowering pathways.

Example 5 Regulation of ANR1 by N

Genetic Effects of a Natural Mutant of ANR1

The functional characterization of the ANR1 gene in normal wheat and transgenic plants provided further evidence that ANR1 and VRN1^N function in the same N metabolism pathway. When conserved primers for homologous ANR1 genes were designed to test expression profiles, ANR1 transcripts were found not in leaves but predominantly in roots in Jagger, but PCR products with different sizes were observed in the root cDNA samples of cultivar 2174. In order to determine if the variable cDNA products were caused by an exon skipping event or by a deletion event at the gDNA level, we cloned the ANR1 cDNA from 2174 (FIG. **23**A). Further sequencing results indicated that an 84 bp-exon 6 was missing in the PCR products of one homologous ANR1 gene from 2174. By sequence comparison, we found that the smaller ANR1 cDNA product in the 2174 allele was caused by a 23-bp deletion event involving an AG splice site at the 5' end of intron 5 in 2174 (FIG. **23**C). The 23-bp deletion included 10 bp in intron 5 and 13 bp in exon 6. The absence of the AG splice site results in the loss of the full exon 6 of 84 bp in the cDNA products.

Based on the polymorphism of 23 bp indel, a PCR marker for ANR1 was developed (FIG. **23**B). ANR1 was mapped to chromosome 2A in bread wheat. When the phenotypic data used to map QNue.osu-5A were analyzed for the genetic effects of ANR1 in the RIL population, the 2174 allele for the 23 bp deletion in the non-functional ANR1b gene was associated with early heading, whereas the Jagger allele for the functional ANR1a gene was associated with late heading, with a difference of 3.7 days between the two alleles. The result suggested that the functional Jagger ANR1a gene may be a repressor for flowering in wheat.

Regulation of ANR1 Transcripts by N in Normal Wheat and Transgenic Wheat Plants

RNAi was used to interfere with ANR1 expression using Jagger as the host plant. Three individual transgenic plants were successfully generated, and their T_1 populations were tested in the yellow soil type used to discover QNue.osu-5A. Like VRN1". ANR1 transcript levels were down-regulated in positive plants compared with non-transgenic plants, and VRN1" transcript levels were further down-regulated by N in the positive plants compared with non-fertilized positive plants (FIG. **23**D). Unlike VRN1^N, ANR1 showed a repressive effect on flowering in transgenic plants, with a difference of 2.5 days for positive plants compared with non-transgenic plants. The heading date of non-transgenic plants was 2.5 days earlier days, compared with non-transgenic plants. A typical positive plant carrying ANR1::RNAi also showed reduced plant size compared with a non-transgenic plant (FIG. **23**E). These results provided direct evidence that ANR1 functioned in the N metabolism and flowering pathways.

Example 5. Significance and Impact

Wheat is one of the most important economic crops worldwide. The United States produces approximately 11% of the world supply and nearly 35% of world exports. Between now and the year 2050, the human population of around 6 billion people is expected to increase to 9 billion. Therefore, the challenge for the next decades will be to accommodate the needs of the expanding world population by developing a highly productive agriculture.

Application of N fertilizers is the most direct and efficient approach to increase wheat production, and thus the addition of excess amounts of N is usually considered as a type of yield insurance, particularly in developed countries. While the purchase of this "insurance" cannot be totally avoided, it is important to search for genotypes that are able to absorb and accumulate high concentrations of N more efficiently. On the other hand, in developing countries which lack natural resources and cannot afford the cost of fertilizers, N is often the most yield limiting nutrient. To develop wheat varieties carrying high NUE genes is a viable strategy to increase economic income in wheat production worldwide.

Strategies for optimized use of N via soil and fertilization management in wheat have been developed and promoted by universities and scientists, laying a foundation for a complementary study of better use of N via genetic improvement. Over the past century, genetics, through the pyramiding of favorable alleles in a single genotype, has proven to be far and away the most powerful tool for improving stress tolerance and yield potential. Novel genomic and computational tools will hasten the progress of gene discovery and accelerate plant improvement to enhance yields. In the previous Examples, we have described how the gene network for genetic improvements of NUE and grain yield is established in wheat.

A simple definition of NUE is crop yield/N supplied, but NUE is a complex trait and many genes could be involved in biological processes for this trait. A key focus is on the starting point to enter the gene network for the complex process by cloning a large QTL for NUE. We have mapped the large QTL in the wheat genome itself, and candidate genes are identified by comparative genomics with the cereal model species rice. Gene function is tested by comparison with orthologous genes characterized in the model plant *Arabidopsis*. This streamlined approach facilitates cloning and characterization of agronomically important genes in wheat breeding and transgenic wheat.

NUE genes have extensive use in agriculture, environment, and industry. First, increased cereal yields are needed to feed a growing world population. Cereal crops have not yet fulfilled their promise with respect to increasing yields via N-fixation, and thus high amounts of supplemental N are required for high cereal yields to attain significant economic income. Currently, most crop plants utilize only 30-35% of added N fertilizer. If even a 1% increase in NUE is obtained in the world, then grains yield would markedly increase by million tons without additional cost, or the same yield could be obtained with a multi-million dollar decrease in fertilizer costs. Second, the inefficient use of large amounts of N fertilizers in agriculture causes significant and potentially irreversible environmental damage, which will lead to a diminished capacity for sustained productivity and deteriorated ecosystems. This consideration makes it essential to attempt to increase yield by other approaches not currently available such as enhancing NUE in an economically and environmentally sustainable fashion. Sustainability of agricultural production refers to our ability to meet current needs for natural resources, products or manufactured goods while preserving the capacity of future generations to meet their needs. Finally, knowledge and genes which improve NUE in wheat can be applied in the production of other crops. For example, biomass from plants such as switchgrass has been proposed to produce ethanol to replace fossil energy. Switchgrass can grow in nutrient poor soils, and a genotype that has a larger capacity to produce biomass with a minimal amount of N fertilizer in marginal lands (e.g. switchgrass that is genetically engineered to contain and express one or more genes related to NUE) is another interesting economic and environmental challenge.

QNue.osu-5A explains a large part of the total phenotypic variation in several N utilization traits. For instance, it accounted for 38.5% and 55.3% of the total variation in grain yield, when the population of plants was initially grown in N-deficient soil and then fertilized with two different levels of N. The gene TaNUE1 could be allelic to the genetic locus that accounted for 13.6% and 22.5% of the total phenotypic variation respectively in leaf GS activity and flowering time in the Chinese Spring×SQ1 population (Habash et al. 2007). However, the presently identified gene population has a larger segregation and the gene(s) is/are cloned from locally adapted winter wheat cultivars. These advantages provide a unique opportunity for the cloning, characterization, and manipulation of TaNUE1 for production of wheat throughout the world.

In summary, experimental evidence provided herein demonstrates that $VRN1^N$ is TaNUE1 at QNue.osu-5A in bread wheat, as shown by genetic association of $VRN1^N$ and TaNUE1, direct interaction of $VRN1^N$ and ANR1, and regulation of $VRN1^N$ and ANR1 by N in normal and transgenic wheat plants. When N fertilizer was utilized, both $VRN1^N$ and ANR1 were down-regulated. HOX1 can be used to promote development, due to its interaction with $VRN1^N$. Therefore, $VRN1^N$ competes with HOX1 in the vernalization pathway and ANR1 in the N metabolism pathway. Molecular markers for these genes developed herein can be used for pyramiding these N genes/alleles in novel wheat cultivars.

Thus, the present invention is well adapted to carry out the objectives and attain the ends and advantages mentioned above as well as those inherent therein. While presently preferred embodiments have been described for purposes of this disclosure, numerous changes and modifications will be apparent to those of ordinary skill in the art. Such changes and modifications are encompassed within the spirit of this invention as defined by the claims.

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cctaggatca atgttagctc atatttattt gaaaataagc caccactaag cctgataata 480

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<210> SEQ ID NO 5
<211> LENGTH: 1841
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 5

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<210> SEQ ID NO 6
<211> LENGTH: 1841
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 6

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<211> LENGTH: 5612
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 7

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<212> TYPE: DNA
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cgacaacact ggcacgcacg ctactgcaga tgcatacaaa ttaagctgca gaacattgca 420

agcaccggaa catttaccac ctggatcaag ctttttttaga cttctaaaaa tgttaaaaaa 480

gaacttgcaa gtggcaacac gcgcgtagga aaagtaaaaa attgacgtga gattgtaccg 540

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acatgtccta agcttaattg cctctgtttc atcatttaat caaataactt gggtgacatg 720

catatgcagg ctgctgctgg gcgttctcgg cggtggcggc ggtggaaggg ctgaccaaga 780

tccgcacggg gcggcttatg tcactgtcgg agcagcagct ggtggactgc gacgtgaacg 840

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gcggcggcct caccacggag tcgtcctacc cgtaccgcgg cacggacggg tcgtgccgcc 960

gctcggcctc ggccgcgtcc atccgtgggt acgaggacgt gccggccaac aacgaggcgg 1020

cgctgatggc ggtcgtggcg caccagcccg tgtccgtggc catcaacggc ggcgacagtg 1080

tgttccggtt ctacgacagc ggcgtgctgg gcgggtccgg ctgcggcacg gagctcaacc 1140

acgccatcac ggcggtcggg tacggcacgg cgagcgacgg cagcaagtac tggatcatga 1200

agaactcgtg ggcacgtcg tggggcgagc gcggctacgt caggatccgc cgcggggagc 1260

gcggcgaggg cgtctgcggc ctcgcccagc tcgcgtcctc cctgtctag 1309

<210> SEQ ID NO 12
<211> LENGTH: 1314
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 12

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gatgccatcg ccgtcgacgc tgccatggtg tcgaggcacg agaagtggat ggcggagcac 180

gggcgcacgt acgccgacga ggaggagaag gcgcggcggc tggaggtatt cctcgccaac 240

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agcaccggaa catttaccac ctggatcaag ctttttttaga cttctaaaaa tgttaaaaaa 480

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aggagtcagc gttcacttta cttcaatgat tggagtatca ttcttaattt tccatttcgg 660

acatgtccta agcttaattg cctccgtttc atcatgtact aatccaataa ctttgggtga 720

catgcatatg caggctgttg ctgggcgttc tcggcggtgg cggcggtgga agggctgacc 780

aagatccgca cggggcggtt ggtgtcgctg tcggagcagc agctggtgga ctgcgacgtg 840

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atgaagaact cgtggggcgc gtcgtggggc gagcgcggct acgtcaggat ccgccgcggc 1260

gtgcgcggcg agggcgtctg cggcctcgcc cagctcgcgt cctaccctgt ctag 1314

<210> SEQ ID NO 13
<211> LENGTH: 907
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 13

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tgcggggaag acgagccgcg ccggagtgac gtcgtacggc ttcccgttcc cctctcggtt 120

tcccgacgcc tctcttggct cacccgcccg cccgccgccg ccctgccact tcctccgcgc 180

gtgaaagccc accgcctatt ccccttccct tcgctctccg acgccgggcg ccaccccggc 240

ggatcgagcg ggcgggcggt tagttagttg cgcatcgctg ttgcttgctt cttctaccgt 300

ttggcgcagg gaggaggagc gtgggggtaa catcgctgtc ccactcccac ccgggtgctg 360

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tcccgtcgat tcctcctccg cccatttgcc cctccgcgtc gcagaatccc ccgcgccacc 540

gctgctgacc gtcgcgccgt agggggaggg gcaggagcga ggagcctagc tcgggggtgg 600

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cgcgggggag ctcggcgcgc tccaagcaca gcgagcgggt ggtggcgcag acgcccgtgg 720

acgcgcgcct gcacgccgag ttcgagggct cgcagcgcca cttcgactat tcctcctcgg 780

tcagcgcgct caaccgctcc ggggccagca ccagctccgc cgtctccgcc tacctccaga 840

acatgcagcg gggccgctac atccagccct tcggctgcct gctcgcgatc cacccggagt 900

ccttcgc 907

<210> SEQ ID NO 14
<211> LENGTH: 907
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 14

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tgcggggaag acgagccgcg ccggagtgac gtcgtacggc ttcccgttcc cctctcggtt 120

tcccgacgcc tctcttggct cacccgcccg cccgccgccg ccctgccact tcctccgcgc 180

gtgaaagccc accgcctatt ccccttccct tcgctctccg acgccgggcg ccaccccggc 240

ggatcgagcg ggcgggcggt tagttagctg cgcatcgctg ttgcttgctt cttctaccgt 300

ttggcgcagg gaggaggagc gtgggggtaa catcgctgtc ccactcccac ccgggtgctg 360

ccccctcctg ttcccttctc actcactgcg tgtgcttatc cgcgccgggc gaatccaatc 420

ccccactctc ccccgtcctt ctccagaaaa gtcgcggctt tccccccgcc ccctcatgat 480

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tcccgtcgat tcctcctccg cccatttgcc cctccgcgtc gcagaatccc ccgcgccacc    540

gctgctgacc gtcgcgccgt agggggaggg gcaggagcga ggagcctagc tcgggggtgg    600

tcgtggtggc gaccggcggc gagatgtcgt cgtcgcggtc caacaaccgg ccggcgtgct    660

cgcgggggag ctcggcgcgc tccaagcaca gcgagcgggt ggtggcgcag acgcccgtgg    720

acgcgcgcct gcacgccgag ttcgagggct cgcagcgcca cttcgactat tcctcctcgg    780

tcagcgcgct caaccgctcc ggggccagca ccagctccgc cgtctccgcc tacctccaga    840

acatgcagcg gggccgctac atccagccct tcggctgcct gctcgcgatc cacccggagt    900

ccttcgc                                                              907
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<210> SEQ ID NO 15
<211> LENGTH: 949
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 15

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cacgcgctct ccttcctcgc cgacctcaag ctcggccact acatgaagat cccgccacgc    180

tgcatgtaca ccgcccaggt acgtgacaga gatcgatctc tcagccccca caatgcacta    240

gatgctcatc actcgctgaa ctaaccggcg tgcgcttggc cggtgcagct ggtgggcacg    300

gtggtcgccg gcgtggtgaa cctggcggtg gcgtggtgga tgctggacag catcgacaac    360

atctgcgacg tggaggcgct gcacccggac agcccctgga cgtgccccaa gtaccgggtc    420

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gggttgtacc ggaacctggt gtggctgttc gtggtcggcg ccgtgctgcc ggtgccggtg    540

tggctgctga gccgggcgtt cccggagaag aagtggatcg cgctcgtcaa cgtgcccgtc    600

atctcctacg gcttcgccgg gatgccgccg gccacgccca ccaacatcgc cagctggctc    660

gtcaccggca ccgtcttcaa cttcttcgtc ttcaggtacc gcaaggggtg gtggcagaag    720

tacaactacg tgctatcggc ggcgctcgac gccggcaccg ccttcatggg ggtgctcatc    780

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tgcccgctcg ccacctgccc caccgcgccc ggcatcgtcg tcaagggctg cccggtcttc    900

tgagcactga gctcgccgga gcatcatcgg acactgcccg ccatgtatg                949
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<210> SEQ ID NO 16
<211> LENGTH: 948
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 16

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cacgcgctct ccttcctcgc cgacctcaag ctcggccact acatgaagat cccgccacgc    180

tgcatgtaca ccgcccaggt acgtgacaga gatcgatctc tcagccccca caatgcacta    240

gatgctcatc actcgctgaa ctaaccggcg tgcgcttggc cggtgcagct ggtgggcacg    300

gtggtcgccg gcgtggtgaa cctggcggtg gcgtggtgga tgctggacag catcgacaac    360

atctgcgacg tggaggcgct gcacccggac agcccctgga cgtgccccaa gtaccgggtc    420

accttcgacg cgtcggtgat ctggggcctc atcgggccgg ggcgcctctt cggccagcac    480
```

```
gggttgtacc ggaacctggt gtggctgttc gtggtcggcg ccgtgctgcc ggtgccggtg    540

tggctgctga gccgggcgtt cccggagaag aagtggatcg cgctcgtcaa cgtgcccgtc    600

atctcctacg gcttcgccgg gatgccgccg gccacgccca ccaacatcgc cagctggctc    660

gtcaccggca ccgtcttcaa cttcttcgtc ttcaggtacc gcaaggggtg gtggcagaag    720

tacaactacg tgctatcggc ggcgctcgac gccggcaccg ccttcatggg ggtgctcatc    780

ttcttcgcgc tccagaacgc gcaccacgac ctcaagtggt ggggcaccga ggtcgaccac    840

tgcccgctcg ccacctgccc gaccgcgccc ggcatcgtcg tcaagggctg cccggtcttc    900

tgagcactga gctcgccgga gcatcatcgg acactgcccg ccatgtag                 948
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<210> SEQ ID NO 17
<211> LENGTH: 884
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 17

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acatgcctct gggaggctct tgaaatacaa tcccgaaaca aaggagacaa cagtccttca    120

ccgcaacctc cagtttccca acggagtgag cttaagcaag gatggctcgt tcttcgtctt    180

ctgtgaagga tctcgtggaa ggtctataca ctcttccctc catttggttc aggatttcat    240

acatgtatac ttgaaattag tcactgatta ttgtgtcctt atccaaacag gttgagcaga    300

tactggctga aaggtgagaa ggcaggcacc gtcgatctct tcgccatcct gcctgggttc    360

ccggacaacg tgaggaccaa cgacaagggc gaattctggg tggccatcca ttgccgacgc    420

agcgcatacg cccggctctt gagtcgccgc gtccagctca gaaagttctt gctcagcctc    480

ccgatccccg ccaagtatca ctacctgatg caaatcggcg gcaatctgca cgcgctcatc    540

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gtgagagctg tgagcgaagt ggaggagaag gatggcaagc tctggatagg atctgttctc    660

atgcccttca ttgccgtctt tgactacgcc aaggaatcct aagccgccct tttgccggga    720

tacatgggta agagagtatg aaatccacga acgccgttgc acactattgc ttcatccaaa    780

taaatctagt gttggaagca acctagaatt gcttgatgtt tcagcctttt cctagtagca    840

actgtaactc actgacattt tagtttgtcc ctgggatctt tcaa                     884
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<210> SEQ ID NO 18
<211> LENGTH: 886
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 18

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agatgcctct gggaggctct tgaaatacaa tcccgaaaca aaggagacaa cagtccttca    120

ccgcaacctc cagtttccca acggagtgag cttaagcaag gatggctcgt tcttcgtctt    180

ctgtgaagga tctcgtggaa ggtctataca ctcttccctc catttggttc agaatttcat    240

acatgtatac ttgaaattag tcactgatta ttgtgtcctt atccaaacag gttgagcaga    300

tactggctga aaggtgagaa ggcaggcacc gtcgatctct tcgccatcct gcctgggttc    360

ccggacaacg tgaggaccaa cgacaagggc gaattctggg tggcaatcca ttgccgacgc    420

agcgcatacg cccggctctt gagtcgccgc gtccagctca gaaagttctt gctcagcctc    480
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ccgatccccg ccaagtatca ctacctgatg caaatcggcg gcaatctgca cgcgctcatc 540

atcaagtaca gccctgaagg cgaggtgctt gacatcttgg aggacactaa agggcaggtg 600

gtgagagctg tgagcgaagt ggaggagaag gatggcaagc tctggatagg atctgttctc 660

atgcccttca ttgccgtctt tgactacgcc aaggaatcct aagccgccct tttgccggga 720

tacatgggta agagagtatg aaatccacga acgccgttgc acactattgc ttcatccaaa 780

ataaatctag tgttggaagc aacctagaat tgcttgatgt ttcagccttt tcctagtagc 840

aactgtaact cactgacatt ttagtttgtc cctggggatc tttcaa 886

<210> SEQ ID NO 19
<211> LENGTH: 9611
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 19

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gtggatttcc ctctggctga atttgtcccc caccccaccc gctcacccac actcgcgtga 180

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ttgtgttaag ggaaaaacaa aggatttttt ttcaagaggt ttgagtggat gctagaattt 420

ctgtgaaatg tagtacaaat gaaccottag aaaaaaatac aggattcaat cctacgaatc 480

aaacgatcaa cgtagaaaaa attcctaagg attctaatcc ttcaaagatc ttatgaaaat 540

cctttgaatc aaagagacct tgaagttgtg gagctcaaaa tttatagtat tcctctagaa 600

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cagggcccac ccgcagcaaa ttgcttctat tatggtggcc gcctcctctc ctctccctgg 780

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tcccctagcg cattcaaatg ggatcaagct aatggcacat tcagtccact tatgtttgat   4260
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<210> SEQ ID NO 21
<211> LENGTH: 4496
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 21

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catatctact ttatggcatg aaaattttga tgtcattgta aaaaagaact ctagccgaag 540

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gaataaaaac catgaacaag tagcagttta ctggttagaa cgccaatttt ttggcttcag 840

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gtggaatctc taaaaagact tatatgtagg aaccgaggga gtatatccaa tctgccatta 4140

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<210> SEQ ID NO 22
<211> LENGTH: 4487
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 22

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gggatgacat agattaagag aaagaagaag atgaatatga cacatggacc cgcgtagtta 180

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tatttaatta acatatcttg tgcactcacc aatgtggttt ctcaattgtt cactttgttt 480

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<210> SEQ ID NO 23
<211> LENGTH: 2318
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 23

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<210> SEQ ID NO 24
<211> LENGTH: 2318
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 24

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tcccgcccac ggcggtggac tccgtgagga agacgcacga agagaactcc cggcgagtcg 360

tgtccgtcgc gctcgacgtg tgcaggcaga agcaggtgag cgccacggcg gcggtggtgg 420

agggcgacgc caaggaggcc atctgccgcg ccgtggagga catgcacgcc gacctcctcg 480

tcctcggcag ccgcggcctg ggcatgatca agaggtacgc gcatgccaat gagatcacca 540

cgcgtgagca tcttcgataa cagattgtga ttctgggtgc agttcgacta cttcactggc 600

agagccaaaa atactaaagc acagcttagc tttcttcagt gttcaagcga cttgaattgc 660 aaacatatgg aaatccttaa atttcaaaat ttcaatgctt gatttggttg gggtttgcca 720

ggtccaggca gtagtgcaac gcctggacga cacatgagag ccctggcagc aagctaccgt 780

gatgggctct cccccataaa aaataaattt aatatcgttg tggacacatg gtccacatat 840

cagatattaa actgataaga acagatacta cacttgatct tagccaaaag gccgagaaag 900

gtatgagttg gaacattgag ctgggtctcg ttttatagcc atctttcccc agggtttctc 960

ctccgtccgc gatgtggtac taaacctgct actgccctct cttctatgct ccggcaatgc 1020

cacccgctgc tcggttgggc ccaaaccgag agcccgtagc aggccttacc gagtcacgtc 1080

atgggctttt ctgttcctgt tcctttttcc attctctctc ttgcagcttg cctcctcttc 1140

tgcttttccc tttgtgcctt cccttcttat cctggtagca tattgaaatg catggctgga 1200

agatgtgcaa tagctagtta acttgcctcc ttaaacagta gtacatttaa gaaaatccaa 1260

tggctaaaga aaacacagtt gtttttagt ttttcatgtt tatttactat gagagcaagc 1320

ctttatcacc gagacaatag tcatgttgct tgcagagtta caagcatatg cataataaaa 1380

ctccatggat catcaagcca cgccttgacc ctgtgcttgt gctggtggtg tgttgcaggg 1440

cgttgctggg cagcgtgagc gactacctcg cccatcacgc ctcctgcccc gttctcatcg 1500

tgaagccgcc cagcaaggcg caccacaagt gaagctccaa ctctgctgcc actgtcgact 1560

gaatgtctcg agtgcctcgt gcttccaata aagatgtgat cgagctcatg tgcagtactc 1620

tatgaacatc ctagaatgta gggaataaac tgttgtttgg ccgcaagcac ttgctgaaat 1680

ttttaatctt ggttagtgca gttgttccga tgcattacat tgccatggac gtagtgttct 1740

ttcttccttg aagtacagag tgcggtgatg ctgctgaaaa acaggcacat ctcgaagagt 1800

tcggttcgcc aaacacatga ccagtacaag acctattgat cacaaatact ccataattcg 1860

ctctaaaaaa cgtattcaga attcctattc ataatgcaga gcatgaatga ccgtcgaagc 1920

atgttctgtt tctaagcaag catgcttttg ttttaaaatg gagacaaaag ttttgcctcg 1980

tctatttaat gaagaagagg gtagagttct gtattacaag gccgcgaggc ccacccgcaa 2040

taaacatgga attactctcc tgatagaatg tttcccaaaa taacaaaatt gcatctgcca 2100

agacccaaag cttggtctag tctttgatgg ccttgagcaa gatggtcttc ggcttgctct 2160

attctcgaaa cacacgggca tttctctcgt ttcaaatggt ccaactaatg agcattgtaa 2220

gcgacgccat tgctttacag ttgaccttgt tgttgcggaa agattgaccc accaatcttt 2280

gttggggctc ttaaggcgcc aagaggaggt tcaaagtt 2318

<210> SEQ ID NO 25
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 25

gcttctcctg gaagctgccg cggacgtggg tcaggtcggt cgaccagctg cccatgaatt 60

acggcgacaa gctctacgac ccgctcttcc ccttcggctt cggcctcacc accaagccgg 120

cggcggatag caggtagcta ggagtctgag tttcttttcc tgccctagtt agtgtgcgat 180

taattagtga gtccgtgagt agtgagaatc ggaaataaat gaggaggata tggttttgat 240

tgcgtcgccc tgtaactgta agttcgctac gaacatccga tgaacttgaa atcaatctat 300

atatagtgct gtcggaattc agtctatctt aattctcgac ttctcgagtc ggtt 354

<210> SEQ ID NO 26
<211> LENGTH: 354

<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 26

gcttctcctg gaagctgccg cggacgtggg tcaggtcggt cgaccagctg cccatgaatt 60

acggcgacaa gctctacgac ccgctcttcc ccttcggctt cggcctcacc accaagccgg 120

cggcggatag cagctagcta ggagtctgag tttcttttcc tgccctagtt agtgtgcgat 180

taattagtga gtccgtgagt agtgagaatc ggaaataaat gaggaggata tggttttgat 240

tgcgtcgccc tgtaactgta agttcgctac gaacatccga tgaacttgaa atcaatctat 300

atatagtgct gtcggaattc agtctatctt aattctcgac ttctcgagtc ggtt 354

<210> SEQ ID NO 27
<211> LENGTH: 232
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 27

caaacagccg tgacacacaa gaggtacact ttctgaaaac ttccgtcaat aactacttat 60

tttgggtggt gatttcatga agaggccatg gcccaccagg gctaatgtta atactttgta 120

tgttccttta aataatgatg atgatgtatc ttgctttttt aaggacacat attttaaata 180

tggtttatca ggtgccttcc ccagttaata aaacagtgga acctataaat tt 232

<210> SEQ ID NO 28
<211> LENGTH: 238
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 28

caaacagccg tgacacacaa gaggtacact ttctgaaaac ttccgtcaat aactacttat 60

tttgggtggt gatttcatga agaggcgaat gttaatactt tgtatgttcc tttagataat 120

gatgatgatg tagcttgctt ttttaaggac gcatatttta gatatggttt atcaagtgcc 180

ttccccagtt aatataacag tggaacctag aaatttgttt ctccattatt gtcatgcg 238

<210> SEQ ID NO 29
<211> LENGTH: 244
<212> TYPE: PRT
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 29

```
Met Gly Arg Gly Lys Val Gln Leu Lys Arg Ile Glu Asn Lys Ile Asn
1               5                   10                  15

Arg Gln Val Thr Phe Ser Lys Arg Arg Ser Gly Leu Leu Lys Lys Ala
            20                  25                  30

His Glu Ile Ser Val Leu Cys Asp Ala Glu Val Gly Leu Ile Ile Phe
        35                  40                  45

Ser Thr Lys Gly Lys Leu Tyr Glu Phe Ser Thr Glu Ser Cys Met Asp
    50                  55                  60

Lys Ile Leu Glu Arg Tyr Glu Arg Tyr Ser Tyr Ala Glu Lys Val Leu
65                  70                  75                  80

Val Ser Ser Glu Ser Glu Ile Gln Gly Asn Trp Cys His Glu Tyr Arg
                85                  90                  95

Lys Leu Lys Ala Lys Val Glu Thr Ile Gln Lys Cys Gln Lys His Leu
            100                 105                 110

Met Gly Glu Asp Leu Glu Ser Leu Asn Leu Lys Glu Leu Gln Gln Leu
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        115                 120                 125

Glu Gln Gln Leu Glu Ser Ser Leu Lys His Ile Arg Ser Arg Lys Asn
    130                 135                 140

Gln Leu Met His Glu Ser Ile Ser Glu Leu Gln Lys Lys Glu Arg Ser
145                 150                 155                 160

Leu Gln Glu Glu Asn Lys Val Leu Gln Lys Glu Leu Val Glu Lys Gln
                165                 170                 175

Lys Ala His Ala Ala Gln Gln Asp Gln Thr Gln Pro Gln Thr Ser Ser
            180                 185                 190

Ser Ser Ser Ser Phe Met Leu Arg Asp Ala Pro Pro Ala Ala Asn Thr
        195                 200                 205

Ser Ile His Pro Ala Ala Thr Gly Glu Arg Ala Glu Asp Ala Ala Val
    210                 215                 220

Gln Pro Gln Ala Pro Pro Arg Thr Gly Leu Pro Pro Trp Met Val Ser
225                 230                 235                 240

His Ile Asn Gly


<210> SEQ ID NO 30
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 30

Met Gly Arg Gly Lys Ile Val Ile Arg Arg Ile Asp Asn Ser Thr Ser
1               5                   10                  15

Arg Gln Val Thr Phe Ser Lys Arg Arg Asn Gly Ile Phe Lys Lys Ala
            20                  25                  30

Lys Glu Leu Gly Ile Leu Cys Asp Ala Glu Val Gly Leu Val Ile Phe
        35                  40                  45

Ser Ser Thr Gly Arg Leu Tyr Glu Tyr Ala Ser Ser Ser Met Lys Ser
    50                  55                  60

Val Ile Asp Arg Tyr Gly Arg Ala Lys Glu Glu Gln Gln Leu Val Ala
65                  70                  75                  80

Asn Pro Asn Ser Glu Leu Lys Ser Trp Gln Arg Glu Ala Ala Ser Leu
                85                  90                  95

Arg Gln Gln Leu His Asn Leu Gln Glu Asn His Arg Gln Leu Met Gly
            100                 105                 110

Gln Asp Leu Ser Gly Met Gly Val Lys Glu Leu Gln Ala Leu Glu Asn
        115                 120                 125

Gln Leu Glu Ile Ser Leu Arg Cys Ile Arg Thr Lys Lys Asp Gln Ile
    130                 135                 140

Leu Ile Asp Glu Ile His Glu Leu Asn His Lys Gly Ser Leu Val His
145                 150                 155                 160

Gln Glu Asn Met Glu Leu Tyr Lys Lys Ile Asn Leu Ile Arg Gln Glu
                165                 170                 175

Asn Val Glu Leu Gln Lys Lys Leu Ser Glu Thr Glu Ala Val Thr Glu
            180                 185                 190

Val Asn Arg Asn Ser Arg Thr Pro Tyr Asn Phe Ala Val Val Glu Asp
        195                 200                 205

Ala Asn Val Ser Val Asp Leu Glu Leu Asn Ser Pro Gln Gln Gln Asn
    210                 215                 220

Asp Val Glu His Thr Ala Pro Pro Lys Leu Gly Leu Gln Leu His Pro
225                 230                 235                 240
```

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<210> SEQ ID NO 31
<211> LENGTH: 723
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 31

atggggcgcg gcaagatagt gatccggcgg atcgacaact ccacgagccg gcaggtgacg      60

ttctcgaagc ggaggaacgg gatcttcaag aaggccgagg agctgggtat tctctgcgat     120

gccgaggtcg gtctcgtcat cttctccagc accggccgcc tctatgagta cgccagctcc     180

agcatgaagt cagtgataga tcgatatggc cgagccaagg aggagcagca acttgttgca     240

aaccccaact cggagcttaa gttctggcaa agggaggcag caagcttgag acaacaactg     300

cacaacttgc aagaaaatca tcggcagttg atgggacaag atctttctgg aatgggtgtc     360

aaggaactgc aggctctaga aaatcaactg gaaataagtc tgcgttgcat ccggacaaaa     420

aaggaccaaa tcttgattga tgagattcat gaactgaatc acaaggggag tcttgtccac     480

caagaaaaca tggaattata caaaaagatt aacctaattc gtcaggaaaa tgttgagtta     540

cagaaaaagc tctctgagac ggaggcagtg actgaagtta accgaaattc aagaactcca     600

tacaattttg cagttgttga agatgccaat gtttctgttg atcttgaact caattccccg     660

cagcaacaaa atgatgttga gcatactgcg ccccctaaac taggattgca actacatcca     720

tga                                                                   723


<210> SEQ ID NO 32
<211> LENGTH: 226
<212> TYPE: PRT
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 32

Met Glu Ser Asp Cys Gln Phe Leu Leu Ala Pro Pro Pro Arg Met Tyr
1               5                   10                  15

Ala Ala Pro Gly Asp Asp Gly Gln Phe Leu Gln Gln Gln Gln Gln Gln
            20                  25                  30

Leu Ser Gly Gly Gly Ala Gly Glu Arg Lys Arg Arg Phe Thr Glu Glu
        35                  40                  45

Gln Val Arg Ser Leu Glu Ser Thr Phe His Thr Arg Arg Ala Lys Leu
    50                  55                  60

Asp Pro Arg Glu Lys Ala Glu Leu Ala Arg Glu Leu Gly Leu Gln Pro
65                  70                  75                  80

Arg Gln Val Ala Ile Trp Phe Gln Asn Lys Arg Ala Arg Trp Arg Ser
                85                  90                  95

Lys Gln Pro Glu Gln Asp Phe Ala Glu Leu Arg Gly His Tyr Asp Ala
            100                 105                 110

Leu Arg Ala Arg Val Glu Ser Leu Lys Gln Glu Lys Leu Thr Leu Ala
        115                 120                 125

Ala Gln Leu Glu Glu Leu Lys Lys Lys Leu Asp Glu Arg Gln Asp Gln
    130                 135                 140

Ser Ala Ser Cys Gly Gly Ser Cys Ala Val Ala Asp Val Asp Asp Lys
145                 150                 155                 160

Arg Asp Asn Val Ser Ser Cys Val Ala Ala Lys Asp Glu Ser Ala Ala
                165                 170                 175

Pro Ala Ala Asp Val Ser Asp Gly Ser Thr Pro Gly Trp Tyr Glu Tyr
            180                 185                 190

Asp Asp His Leu Val Tyr Gly Val Asp Leu His Glu Pro Phe Cys Ala
        195                 200                 205
```

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Thr Gln Glu Leu Trp Glu Thr Ser Trp Pro Leu Val Glu Trp Asn Ala
    210                 215                 220

Val Ala
225


<210> SEQ ID NO 33
<211> LENGTH: 681
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 33

atggagagcg actgccagtt cctgctggcg ccgccgccgc gcatgtacgc cgcgccgggg      60

gacgacggcc agttccttca gcagcagcag cagcagctga gcggcggcgg cgccggggag     120

aggaagcggc ggttcacgga ggagcaggtg cggtcgctgg agagcacgtt ccacacgcgg     180

cgcgccaagc tggacccccg ggagaaggcg gagctggcgc gcgagctggg gctgcagccg     240

cgccaggtgg ccatctggtt ccagaacaag cgcgcccggt ggcgctccaa gcagccggag     300

caggacttcg cggagctgcg cggccattac gacgccctcc gcgcccgcgt cgagtcgctc     360

aagcaggaaa agctcactct cgccgcgcag ctggaagagc tgaagaagaa gctggacgag     420

cggcaagacc agagcgctag ctgcggcggc tcttgcgccg tcgccgacgt agacgacaag     480

agggataacg ttagcagctg cgtcgcggcg aaggatgaga gcgcggcgcc ggcggcagac     540

gtgtcggacg gctcaactcc gggctggtac gagtatgacg accacctggt gtatggggtt     600

gacctgcacg agccgttctg cgccactcag gagctgtggg agacgtcatg gccgctggtg     660

gagtggaacg cagtggcatg a                                               681


<210> SEQ ID NO 34
<211> LENGTH: 212
<212> TYPE: PRT
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 34

Met Gly Arg Gly Lys Ile Val Ile Arg Arg Ile Asp Asn Ser Thr Ser
1               5                   10                  15

Arg Gln Val Thr Phe Ser Lys Arg Arg Asn Gly Ile Phe Lys Lys Ala
            20                  25                  30

Lys Glu Leu Gly Ile Leu Cys Asp Ala Glu Val Gly Leu Val Ile Phe
        35                  40                  45

Ser Ser Thr Gly Arg Leu Tyr Glu Tyr Ala Ser Ser Ser Met Lys Ser
    50                  55                  60

Val Ile Asp Arg Tyr Gly Arg Ala Lys Glu Glu Gln Gln Leu Val Ala
65                  70                  75                  80

Asn Pro Asn Ser Glu Leu Lys Ser Trp Gln Arg Glu Ala Ala Ser Leu
                85                  90                  95

Arg Gln Gln Leu His Asn Leu Gln Glu Asn His Arg Gln Leu Met Gly
            100                 105                 110

Gln Asp Leu Ser Gly Met Gly Val Lys Glu Leu Gln Ala Leu Glu Asn
        115                 120                 125

Gln Leu Glu Ile Ser Leu Arg Cys Ile Arg Thr Lys Lys Asp Gln Ile
    130                 135                 140

Leu Ile Asp Glu Ile His Glu Leu Asn His Lys Leu Ser Glu Thr Glu
145                 150                 155                 160

Ala Val Thr Glu Val Asn Arg Asn Ser Arg Thr Pro Tyr Asn Phe Ala
                165                 170                 175
```

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Val Val Glu Asp Ala Asn Val Ser Val Asp Leu Glu Leu Asn Ser Pro
            180                 185                 190

Gln Gln Gln Asn Asp Val Glu His Thr Ala Pro Pro Lys Leu Gly Leu
        195                 200                 205

Gln Leu His Pro
    210


<210> SEQ ID NO 35
<211> LENGTH: 639
<212> TYPE: DNA
<213> ORGANISM: Triticum aestivum

<400> SEQUENCE: 35

atggggcgcg gcaagatagt gatccggcgg atcgacaact ccacgagccg gcaggtgacg      60

ttctcgaagc ggaggaacgg gatcttcaag aaggccgagg agctgggtat tctctgcgat     120

gccgaggtcg gtctcgtcat cttctccagc accggccgcc tctatgagta cgccagctcc     180

agcatgaagt cagtgataga tcgatatggc cgagccaagg aggagcagca acttgttgca     240

aaccccaact cggagcttaa gttctggcaa agggaggcag caagcttgag acaacaactg     300

cacaacttgc aagaaaatca tcggcagttg atgggacaag atctttctgg aatgggtgtc     360

aaggaactgc aggctctaga aaatcaactg gaaataagtc tgcgttgcat ccggacaaaa     420

aaggaccaaa tcttgattga tgagattcat gaactgaatc acaagctctc tgagacggag     480

gcagtgactg aagttaaccg aaattcaaga actccataca attttgcagt tgttgaagat     540

gccaatgttt ctgttgatct tgaactcaat tccccgcagc aacaaaatga tgttgagcat     600

actgcgcccc ctaaactagg attgcaacta catccatga                            639
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What is claimed is:

1. A method of producing a plant in which one or more traits associated with nitrogen use efficiency (NUE) are improved, comprising the steps of

genetically engineering said plant to contain and express at least one plant gene TaNUE1 from locus Qnue.osu-5A which is responsible for nitrogen use efficiency (NUE), wherein said at least one plant gene is or includes $VRN1^N$ from wheat cultivar Jagger having the amino acid sequence as set forth in SEQ ID NO: 9, or having an amino acid sequence that is at least 95% identical to SEQ ID NO: 9,

testing the plant for one or more traits associated with NUE, and

selecting the plant if the one or more traits are increased in the plant, compared to plants that have not been genetically engineered to contain and express the at least one plant gene TaNUE1 from locus Qnue.osu-5A which is responsible for NUE.

2. The method of claim **1**, wherein said one or more traits associated with NUE is selected from the group consisting of heading date, chlorophyll content, grain yield, harvest index, nitrogen concentration in grain, spike number per plant, grain number per spike, biomass per plant, and a ratio of grain yield to N supplied.

3. A method of providing a plant cultivar that exhibits increased nitrogen use efficiency (NUE) comprising

crossing a plant cultivar comprising a $VRN1^N$ allele from wheat cultivar Jagger with a plant cultivar that does not comprise the $VRN1^N$ allele from wheat cultivar Jagger;

testing an F1 generation plants produced by said step of crossing for the presence of the $VRN1^N$ allele from wheat cultivar Jagger;

testing the F1 generation plants for one or more traits associated with NUE; and

selecting a plant which tests positive for the presence of the $VRN1^N$ allele from wheat cultivar Jagger and which exhibits an increase in one or more traits associated with NUE.

4. The method of claim **3**, wherein said one or more traits associated with NUE is selected from the group consisting of heading date, chlorophyll content, grain yield, harvest index, nitrogen concentration in grain, spike number per plant, grain number per spike, biomass per plant, and a ratio of grain yield to N supplied.

5. A method of providing a plant cultivar that exhibits increased NUE, comprising

crossing a plant cultivar comprising a ANR1 allele from wheat cultivar Jagger with a plant cultivar that does not comprise the ANR1 allele from wheat cultivar Jagger;

testing an F1 generation plants produced by said step of crossing for the presence of the ANR1 allele from wheat cultivar Jagger;

testing the F1 generation plants for an increase in one or more traits associated with NUE; and

selecting a plant which tests positive for the presence of the $VRN1^N$ allele from wheat cultivar Jagger and which exhibits an increase in one or more traits associated with NUE.

* * * * *